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# The cost effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial.



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**COVER SHEET**

**Title**: The cost effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial.

**Short Title:** The PRINCE Study: Cost Effectiveness Analysis

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## ARTICLE SUMMARY

### Article focus

- Pulmonary rehabilitation is key strategy in the clinical management of chronic obstructive pulmonary disease.
- Little is known about the cost effectiveness of pulmonary rehabilitation for chronic obstructive pulmonary disease delivered in primary care.

### Key messages

- There is conflicting evidence as to the cost effectiveness of a structured education programme for chronic obstructive pulmonary disease delivered in primary care.
- Results vary depending on whether disease-specific or generic measures of health status are used to judge effectiveness: in this study, there was strongly favourable evidence for the former; while no such evidence existed for the latter.
- It is important to calculate incremental cost effectiveness results for both disease-specific and generic outcome measures when conducting economic evaluation of interventions for chronic obstructive pulmonary disease.

### Strengths and Limitations

- Strengths include the study design, the sample size, and the range of resource, cost and economic patient level data collected for analysis.
- Limitations include the time horizon of the analysis which was confined to the trial follow up period, thereby reducing the ability to gauge the longer term effects of treatment.

## ABSTRACT

**Objective:**

To assess the cost effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease (COPD) in primary care.

**Design:**

Economic evaluation alongside a cluster randomised controlled trial

**Setting:**

32 general practice surgeries in Ireland

**Participants:**

350 adults with chronic obstructive pulmonary disease.

**Interventions:**

Intervention arm (n=178) received a structured education pulmonary rehabilitation programme. Control arm (n=172) received usual care in general practice.

**Main Outcome Measures:**

Incremental costs, Chronic Respiratory Questionnaire (CRQ), quality adjusted life years (QALYs) gained, and expected cost effectiveness at 22 weeks trial follow up.

**Results:**

The intervention was associated with mean increases of €944 (95% CIs: 489, 1400) in healthcare cost and €261 (95% CIs: 226, 296) in patient cost. The intervention was associated with a mean improvement of 1.11 (95% CIs: 0.35, 1.87) in CRQ Total score and 0.002 (95% CIs: -0.006, 0.011) in QALYs gained. The probability of the intervention being cost effective at respective threshold values of €5,000, €15,000, €25,000 €35,000, and €45,000 was 0.980, 0.992, 0.994, 0.994, and 0.994 in the CRQ Total score analysis compared to 0.000, 0.001, 0.001, 0.003, and 0.007 in the QALYs gained analysis.

**Conclusions:**

There is conflicting evidence as to the cost effectiveness of a structured education pulmonary rehabilitation programme for COPD delivered in primary care. While strongly favourable results exist when health status was measured using the disease-specific CRQ instrument, no

evidence exists when effectiveness was measured in QALYS gained, estimated using the generic EQ5D instrument.

**KEY WORDS**:
COPD; Pulmonary Rehabilitation; Structured Education; Cost Effectiveness

**TRIAL REGISTRATION:**
Current Controlled Trials ISRCTN52403063

## INTRODUCTION

Pulmonary rehabilitation is key strategy in the clinical management of chronic obstructive pulmonary disease (COPD) and has been shown to be effective in improving patients' health related quality of life.[1, 2, 3] While much of the established evidence relates to programmes delivered in hospital, outpatient, or home settings,[4] there are growing calls for the provision of such services in the primary care setting.[5, 6] Nonetheless, further evidence on clinical and cost effectiveness is required before primary care provision can be recommended.

The PRINCE study sought to examine the clinical and cost effectiveness of pulmonary rehabilitation for COPD delivered at the level of general practice in Ireland.[7] Full details of the study methods are published elsewhere.[7] In brief, a cluster randomized controlled trial (RCT) recruited 32 general practices and 350 patients with a diagnosis of COPD as defined by the GOLD guidelines.[8] Ethical approval was provided by the local ethics committees at the participating study centres. Practices were randomised to the control group, where patients (n=172) received usual care in general practice, or the intervention group, in which patients (n=178) received a structured education pulmonary rehabilitation programme (SEPRP). The SEPRP consisted of an eight-week programme with a two-hour session each week delivered jointly by a practice nurse and physiotherapist at the practice surgery of venue nearby. The practice nurse facilitated the educational content of the programme and the physiotherapist focused on delivering the exercise component. The practice nurse also provided on-going advice and support to participants as required throughout the intervention period. In addition, participants were followed-up formally via telephone call at 4 weeks after completion of the SEPRP and via a 1-hour group session at 10 weeks. To facilitate the delivery of the intervention, educators received training via specialised preparation programmes and on-going support from the research team. To ensure standardisation of programme content and delivery, all training was provided by research staff, and educators were audited to ensure adherence to programme principles and content.

Details on the characteristics of the study participants are presented in Appendix Table 1 and were broadly similar across treatment arms.[9] Two patients in the intervention group and 6 patients in the control group died over the course of the trial, leaving 342 (98%) for the statistical analysis.[9] The primary outcome in the clinical analysis was change in disease-specific health status from baseline to follow up, as measured using the Chronic Respiratory

Questionnaire (CRQ).[10] At trial follow up, the intervention was associated with statistically significant improvements in CRQ Dyspnoea scores (0.49; 95% CIs: 0.20, 0.78), CRQ Physical scores (0.37; 95% CIs: 0.14, 0.60), and CRQ Total score (1.11; 95% CIs: 0.35, 1.87) relative to the control.[9] Notably however, concerns arose as the confidence intervals did not exclude differences in effect that were pre-specified as clinically insignificant.[9]

In addition to clinical effectiveness, any decision regarding the adoption of a healthcare intervention in clinical practice will depend upon its expected cost effectiveness.[11] To this end, this study explores the cost effectiveness of the SEPRP intervention based on evidence collected alongside the cluster RCT. The technique of economic evaluation compares the relative cost effectiveness of alternative treatment strategies by relating their mean differences in cost to their mean differences in effectiveness, and by quantifying the uncertainty surrounding these incremental point estimates. Central to this process is the selection of suitable outcome measures which enable the detection of clinically important treatment effects. In addition, and in order to more fully inform priority setting, generic outcome measures are preferable as they enable the comparison of a wide range of programmes across multiple patient populations, all of which may be competing for limited healthcare resources. Notably however, recent evidence has cast doubt on the ability of generic outcome measures to adequately capture meaningful differences in clinical severity for COPD patient populations.[12] Indeed, the adoption of generic rather than disease-specific measures in this context may lead to the underestimation of treatment benefits, biased cost effectiveness results, and ill-informed policy decisions.[13] With this in mind, we present and compare cost effectiveness results for disease-specific health status, as measured by the CRQ instrument, and generic health status, as measured by quality adjusted life years (QALYs) gained.

## METHODS

### Overview

The economic evaluation consisted of a trial-based analysis with a time horizon of 22 weeks, the trial follow up period. The perspective of the healthcare provider and the patient was adopted with respect to costing and health outcomes were expressed in terms of disease-specific and generic health status. Evidence on resource use and health status was collected via structured questionnaires and practice note searches at baseline (for the 26 weeks pre-

randomisation) and follow up. The statistical analysis was conducted on an intention to treat basis, and in accordance with current guidelines for clinical and cost effectiveness analysis alongside cluster RCTs.[14, 15] That is, we adopt statistical techniques which recognise both the clustering and correlation of cost and effect data. The incremental analyses were undertaken using generalised estimating equations (GEE), a flexible multivariate regression framework that explicitly allows for the modelling of normal and non-normal distributional forms of clustered data.[16] Uncertainty in the analysis was addressed by estimating 95% confidence intervals and cost effectiveness acceptability curves, which link the probability of a treatment being cost effective to a range of potential threshold values (λ) that the health system may be willing to pay for an additional unit of effect.[11] All analysis was undertaken using STATA and EXCEL statistical packages.

**Cost Analysis**

Three cost components were included in the analysis, all of which were expressed in Euros (€) in 2009 prices. The first was the cost of implementing the intervention in clinical practice and included resources relating to: educator and patient recruitment; educator, administrator and patient time input; venue and equipment rental; educational materials and consumables; and post, packaging, telephone and travel expenses (see Appendix Table 2). Second, costs relating to the use of primary and secondary healthcare services over the course of the trial were estimated. This included the costs of general practitioner (GP), practice nurse, physiotherapist, dietician, public health nurse, home help, and social worker consultations, outpatient services, accident and emergency (A&E) visits, hospital admissions, COPD medications and oxygen therapy. Third, private costs to patients, in terms of time input and travel expenses over the course of the trial, were included.

A vector of unit costs was applied to calculate the cost associated with each resource activity at baseline and follow up (see Table 1). Unit cost estimates for each activity were based on national data sources and, where necessary, were transformed to Euros (€) in 2009 prices using appropriate indices.[17,18] Two total cost variables were constructed for the incremental analysis: (i) total healthcare cost and (ii) total patient cost. To facilitate this process, imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing values for individual resource use at follow up. Estimation of incremental costs at follow up was undertaken using GEE regression models controlling for treatment

arm, baseline cost, and clustering. To account for the non-normal nature of the cost data, multilevel regression models assuming a gamma variance function were estimated.[19]

**Effectiveness Analysis**

Health outcomes in the analysis were expressed in terms of disease-specific and generic measures of health status. COPD-specific health status was measured using the CRQ instrument,[10] which consists of 20 items which are subdivided into four domains: dyspnoea, fatigue, emotional function and mastery. Based on patient responses, three CRQ aggregate scores can be calculated: (i) CRQ Physical, which combines the dyspnoea and fatigue domains; (ii) CRQ Psychological, which combines emotional function and mastery domains; and (iii) CRQ Total, which combines all four domains. For the purposes of the economic evaluation, only the CRQ Total score variable was included in the incremental cost effectiveness analysis.

Generic health status was expressed in terms of QALYs gained calculated using the area under the curve method,[20] and based on patient responses to the EuroQol EQ5D instrument.[21] The EQ5D consists of five dimensions: mobility, self-care, usual activities, pain or discomfort and anxiety or depression, and each dimension has three levels of severity: no problems, moderate problems or extreme problems. EQ5D responses are transformed using an algorithm into a single health state index score, based on values elicited from the UK population, which typically range from 0 (equivalent to death) to 1 (equivalent to good health), although a small number of health states are valued as worse than death. EQ5D scores at baseline and follow up were used to calculate patient-specific QALYs gained over 22 weeks. To facilitate this process, imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing values at follow up. Estimation of incremental effectiveness at follow up was undertaken using GEE regression models controlling for treatment arm, baseline EQ5D score, and clustering.

**Cost Effectiveness Analysis**

In economic evaluation, one treatment is defined as more cost effective than its comparator if one of the following conditions apply: (a) it is less costly and more effective; (b) it is more costly and more effective, but its additional cost per additional unit of effect, known as the incremental cost effectiveness ratio (ICER), is considered worth paying by decision makers; or (c) it is less costly and less effective, but the additional cost per additional unit of effect of

its comparator is not considered worth paying by decision makers.[11] We employ the net benefit framework,[22] which allows for costs and effectiveness to be combined into a single variable for each individual, to identify which of these three conditions applies in this case. We define net benefit (*nb*) as,

$nbijk = eijk\lambda - cijk$,

where *eijk* is the health outcome for the ith person in the jth cluster in treatment arm *k*, λ is the cost effectiveness threshold value, and *cijk* is their cost. Using this framework, the intervention is defined to be cost effective, at a given threshold value, λ, if its corresponding net benefit is greater than that of the control: that is, if the incremental net benefit for the intervention minus control is greater than zero.

Net benefit statistics for CRQ Total score and QALYs gained were calculated by relating total healthcare costs to the outcome measures of interest for a series of threshold values (ranging from λ = €0 to €70,000). Estimation of incremental net benefit was undertaken using GEE regression models controlling for treatment arm, baseline CRQ or EQ5D score, baseline healthcare cost and clustering. The incremental cost effectiveness results are presented using ICERs and cost effectiveness acceptability curves, which were estimated parametrically,[22] and report the probability that the intervention is more cost effective than the control. The curves incorporate the sampling uncertainty around the ICER estimates as well as the uncertainty around the true threshold value, λ,[23] which is unknown for Ireland.[24]

## RESULTS

Estimates for resource use, costs and health outcomes at follow up are summarised in Table 2 (for baseline results see Appendix Table 3). The cost of the intervention was estimated at €822 per participant, which consisted of €564 in healthcare costs and €258 in patient costs (see Appendix Table 2). In terms of total costs over 22 weeks follow up, the mean healthcare cost per patient in the control arm was €1505 (SD: 1872) and €2357 (SD: 3532) in the intervention arm. The equivalent results for total patient cost were €129 (SD: 113) and €380 (SD: 111) respectively. In terms of disease-specific health status, mean CRQ Total score per patient was 19.10 (SD: 4.83) in the control arm and 20.82 (SD: 3.88) in the intervention arm.

In terms of generic health status, mean QALYs gained per patient at 22 weeks was 0.305 (SD: 0.106) in the control arm and 0.337 (SD: 0.081) in the intervention arm.

The results from the incremental analyses are presented in Table 3. These indicate that the intervention was, on average, associated with higher costs and improved health outcomes, as measured using the CRQ and QALYs, when compared to the control. The intervention was estimated to result in a statistically significant increase in mean cost per patient of €944 (95% CIs: 489, 1400) in total healthcare costs and €261 (95% CIs: 226, 296) in total patient costs. In respect of effectiveness, the intervention was associated with a statistically significant increase in mean CRQ Total score of 1.11 (95% CIs: 0.35, 1.87) per patient and a non-significant increase in mean QALYs gained of 0.002 (95% CIs: -0.006, 0.011) per patient.

These results translated into incremental cost effectiveness ratios of €850 per unit increase in CRQ Total score and €472,000 per additional QALY gained. In terms of expected cost effectiveness, the probabilistic results are summarised in Table 3 and presented graphically in Figure 1. These indicate that for the CRQ Total score analysis, the probability of the intervention being more cost effective than the control was 0.980, 0.992, 0.994, 0.994, and 0.994 at threshold values of €5,000, €15,000, €25,000 €35,000, and €45,000 respectively. For the QALYs gained analysis, the equivalent probability estimates were 0.000, 0.001, 0.001, 0.003, and 0.007 respectively.

## DISCUSSION

On the basis of evidence collected alongside a cluster RCT, a structured education pulmonary rehabilitation programme for COPD delivered in primary care was, on average, more costly and more effective than usual general practice care. Notably however, while the intervention was associated with statistically significant improvements in disease-specific health status, this was not reflected in generic health status. Moreover, the confidence intervals for the disease-specific analysis did not exclude differences in effect that were deemed clinically insignificant.[9] Given the uncertainty relating to the effectiveness data, there is unsurprisingly conflicting evidence regarding the value for money of the programme. While there appears to be strong cost effectiveness evidence when outcomes are measured in terms of disease-specific health status, no such evidence exists in relation to generic health status. More specifically, in the cost per CRQ Total score analysis, the probability that the

intervention was more cost effective than usual care was 0.980 or greater for a range of potential threshold values, notwithstanding concerns relating to clinical insignificance. In stark contrast, the cost per QALY gained analysis indicates that the intervention is highly unlikely to be deemed cost effective relative to usual care or indeed other programmes inside and outside of COPD medicine. As usual, it will ultimately be the remit of the relevant policy decision maker to determine whether the evidence presented is sufficient to justify the adoption of the SEPRP intervention in clinical practice.

This study highlights the complexity of resource allocation decision making in this context as variations in estimated incremental effectiveness have markedly different implications for policy. Indeed, the central question which arises is that of whether our findings reflect an absence of a clinically significant treatment effect or alternatively a lack of sensitivity in the ability of the generic EQ5D instrument to detect a clinically meaningful improvement in COPD health status. In the case of the former, it is also worth noting that in contrast to the majority of trials included in a Cochrane systematic review,[4] most participants in our study had moderate COPD (FEV1 around 55-60% predicted).[9] In the case of the latter, our results highlight the need for a better understanding of the relationship between COPD disease-specific and generic outcome measures, the importance of exploring cost effectiveness in terms of both disease-specific and generic health status for this patient population, and the need to consider both measures in the resource allocation decision making process.

This study adds to the existing literature on the cost effectiveness of pulmonary rehabilitation for COPD by evaluating a programme delivered in primary care. Whereas a broad literature has demonstrated that such programmmes are efficacious in various hospital, outpatient and home settings, the health economic literature, whilst limited,[4, 25] also generally confirms their cost effectiveness.[26-34] The latter evidence is driven not only by their impact in improving patient health, but also in many cases by their impact in reducing healthcare utilisation and costs, particularly in relation to hospitalisation. Notably, those studies which did report cost savings generally adopted time horizons for analysis of up to 1 year or more, while we adopted a follow up of 22 weeks and did not observe a reduction in costs.

There were a number of limitations in this study. The time horizon was limited to the end of the trial and further follow up of study participants is required to gauge the longer term effects of treatment and to explore whether these have a substantive impact on the results

presented. Furthermore, while we employ an appropriate multilevel net benefit regression approach to account for the correlation and clustering in the cost and effect data, arguments could be made for alternative bivariate or non-parametric approaches.[15] The conduct of economic evaluation in Ireland is complicated by a paucity of relevant data. In particular, given the lack of utility data the EQ5D instrument was adopted and assumed to be relevant for an Irish population. Furthermore, as stated above, the EQ5D may not be appropriate for COPD patient populations. Finally, the process of conducting cost analysis in Ireland is complicated by the lack of nationally available unit cost data. In estimating unit costs for individual resource activities, we endeavoured at all times to be conservative in any assumptions adopted.

In conclusion, there is conflicting evidence as to the cost effectiveness of a structured education programme for COPD delivered in primary care. While there appears to be strongly favourable evidence in terms of disease-specific health status, concerns exist as to the clinical significance of the estimated effectiveness improvements, while no evidence exists in terms to generic health status. As a result, uncertainty surrounds the policy implications of this analysis. Nonetheless, the study confirms the importance of calculating incremental cost effectiveness results for both disease-specific and generic outcome measures for COPD patient populations.

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**Table 1 – Categories of Resource Use and Unit Cost Estimates in 2009 (€) Prices**

| RESOURCE ITEM | ACTIVITY | UNIT COST €'s | SOURCE |
|---|---|---|---|
| **Healthcare Resources** | | | |
| General Practitioner | Per Consultation | 50 | ORC |
| Practice Nurse | Per Consultation | 12 | DOHC |
| Hospital Admission | Per Inpatient Day | 832 | DOHC |
| Outpatient Clinic | Per Visit | 169 | DOHC |
| Accident and Emergency Clinic | Per Visit | 289 | DOHC |
| Physiotherapist | Per Consultation | 24 | HSE |
| Dietician | Per Consultation | 24 | HSE |
| Public Health Nurse | Per Consultation | 27 | HSE |
| Home Help Visit | Per Consultation | 16 | HSE |
| Social Worker Visit | Per Consultation | 24 | HSE |
| | | | |
| Spiriva | Per Day | 1.42 | MIMS |
| Seretide | Per Day | 2.22 | MIMS |
| Serevent | Per Day | 0.94 | NICE |
| Ventolin | Per Day | 0.24 | MIMS |
| Combivent | Per Day | 0.83 | MIMS |
| Singulair | Per Day | 1.18 | MIMS |
| Becotide | Per Day | 0.27 | MIMS |
| Symbicort | Per Day | 1.55 | MIMS |
| Pulmicort | Per Day | 0.82 | MIMS |
| Bricanyl | Per Day | 0.21 | MIMS |
| Prednisone | Per Day | 0.47 | MIMS |
| Phyollocntin | Per Day | 0.28 | MIMS |
| Uniphyl | Per Day | 0.19 | MIMS |
| Atrovent | Per Day | 0.20 | MIMS |
| Oxygen Cylinder | Per Day | 4.91 | Britton et al, 2003 |
| Oxygen Concentrator | Per Day | 2.19 | Britton et al, 2003 |
| | | | |
| **Patient Resources** | | | |
| *Travel Expenses* | | | |
| Car | Per Mile | 1.06 | DOF |
| Bus | Per Mile | 1.64 | Dublin Bus |
| Taxi | Per Fare/Add. Mile | 3.71/1.56 | www.taxi.ie |
| *Time Input* | | | |
| Economically Active | Per Hour | 19 | CSO |
| Economically Inactive | Per Hour | 9 | CSO |

**Note 1:**
ORC – Office of the Revenue Commissioner, Dublin, Ireland.
DOHC – Casemix Unit, Department of Health and Children, Dublin, Ireland
HSE – Salary Scales, Health Service Executive, Dublin, Ireland
MIMS - Monthly Index of Medical Specialties Ireland, Dublin, Ireland
NICE – National Institute of Clinical Excellence, London, United Kingdom
DOF – Department of Finance, Dublin, Ireland
CSO – Central Statistics Office, Dublin, Ireland

**Table 2 – Resource Use, Costs and Health Outcomes Estimates at 22 Week Follow Up**

| VARIABLE | INTEVENTION *Mean (SD) / %* | | CONTROL *Mean (SD) / %* | |
|---|---|---|---|---|
| **RESOURCE ITEM** | **Usage** | **Cost (€)** | **Usage** | **Cost(€)** |
| **Healthcare Resources** | | | | |
| GP Visits: Breathing Problems | 1.6 (2.0) | 134 (122) | 1.8 (2.5) | 153 (158) |
| GP Visits: Other | 2.4 (2.5) | 118 (124) | 2.7 (2.7) | 133 (136) |
| Practice Nurse Visits: Breathing Problems | 0.1 (0.3) | 1 (4) | 0.1 (0.5) | 2 (6) |
| Practice Nurse Visits: Other | 1.1 (2.0) | 13 (24) | 1.2 (2.1) | 14 (25) |
| Inpatient Days: Breathing Problems | 0.5 (2.8) | 411 (2300) | 0.1 (0.6) | 80 (504) |
| Inpatient Days: Other | 0.4 (2.5) | 336 (2054) | 0.3 (1.9) | 266 (1552) |
| Outpatient Visits: Breathing Problems | 0.2 (0.5) | 36 (90) | 0.3 (0.7) | 52 (124) |
| Outpatient Visits: Other | 0.8 (1.5) | 134 (253) | 0.7 (1.2) | 118 (208) |
| Accident &Emergency Visits: Breathing Problems | 0.1 (0.2) | 12 (57) | 0.1 (0.3) | 17 (76) |
| Accident &Emergency Visits: Other | 0.1 (0.3) | 23 (78) | 0.1 (0.2) | 16 (66) |
| Physiotherapist Visits: Breathing Problems | 3% | 6 (33) | 2% | 5 (30) |
| Physiotherapist Visits: Other | 6% | 11 (46) | 5% | 11 (45) |
| Public Health Nurse Visits: Breathing Problems | 1% | 3 (27) | 2% | 3 (28) |
| Public Health Nurse Visits: Other | 4% | 8 (42) | 5% | 12 (51) |
| Dietician Visits | 1% | 1(4) | 2% | 1 (6) |
| Home Help Visits | 5% | 63(280) | 7% | 87 (325) |
| Social Worker Visits | 0% | 0 (0) | 1% | 1 (2) |
| Spiriva | 59% | 138 (115) | 62% | 144 (113) |
| Seretide | 56% | 203 (182) | 55% | 200 (182) |
| Serevent | 1% | 2 (16) | 1% | 1 (12) |
| Ventolin | 53% | 21 (20) | 52% | 20 (20) |
| Combivent | 13% | 18 (46) | 15% | 21 (49) |
| Singulair | 9% | 16 (53) | 11% | 21 (60) |
| Becotide | 4% | 2 (9) | 7% | 3 (11) |
| Symbicort | 18% | 45 (97) | 20% | 50 (102) |
| Pulmicort | 4% | 5 (26) | 5% | 7 (30) |
| Bricanyl | 2% | 1 (5) | 2% | 1 (5) |
| Prednisone | 4% | 3 (15) | 11% | 8 (24) |
| Phyollocntin | 1% | 1 (4) | 3% | 1 (8) |
| Uniphyl | 8% | 3 (8) | 7% | 2 (8) |
| Atrovent | 7% | 2 (8) | 8% | 3 (9) |
| Oxygen Therapy | 3% | 16 (96) | 5% | 26 (121) |
| Intervention | n/a | 564 (n/a) | n/a | 0 (n/a) |
| Total Healthcare Cost | n/a | 2357 (3532) | n/a | 1505 (1872 |
| **Patient Resources** | | | | |
| Travel Expenses | n/a | 88 (89) | n/a | 86 (80) |
| Time Input | n/a | 37 (32) | n/a | 39 (32) |
| Intervention | n/a | 258 (n/a) | n/a | 0 (n/a) |
| Total Patient Cost | n/a | 380 (111) | n/a | 129 (113) |
| **HEALTH OUTCOME** | **INTEVENTION** *Mean (SD)* | | **CONTROL** *Mean (SD)* | |
| **Disease Specific Measures** | | | | |
| CRQ Dyspnea Score | 4.42 (1.36) | | 3.85 (1.45) | |
| CRQ Fatigue Score | 4.79 (1.31) | | 4.33 (1.47) | |
| CRQ Physical Score | 4.62 (1.10) | | 4.12 (1.29) | |
| CRQ Emotional Score | 5.62 (1.19) | | 5.24 (1.30) | |
| CRQ Mastery Score | 5.94 (1.11) | | 5.59 (1.30) | |
| CRQ Psychological Score | 5.78 (1.06) | | 5.41 (1.22) | |
| CRQ Total Score | 20.82 (3.88) | | 19.10 (4.83) | |
| **Generic Measures** | | | | |
| EQ5D Score at Baseline | 0.789 (0.209) | | 0.694 (0.296) | |
| EQ5D Score at Follow up | 0.801 (0.232) | | 0.762 (0.252) | |
| QALYs gained | 0.337 (0.081) | | 0.305 (0.106) | |

**Note 1:** See appendix for details on baseline data

**Table 3 – Incremental Analysis**

| VARIABLES | INCREMENTAL ANALYSIS | |
|---|---|---|
| **COST ANALYSIS**<br><br>**Healthcare Resources**<br>Total Healthcare Cost (€)<br><br>**Patient Resources**<br>Total Patient Cost (€) | **Difference in Means (95% CI's)**<br>(Intervention versus Control)<br><br>944 (489, 1400)<br><br>261 (226, 296) | |
| **EFFECTIVENESS ANALYSIS**<br><br>**Disease Specific Measures**<br>CRQ Total Score<br><br>**Generic Measures**<br>QALYs gained | **Difference in Mean (95% CI's)**<br>(Intervention versus Control)<br><br>1.11 (0.35, 1.87)<br><br>0.002 (-0.006, 0.011) | |
| **COST EFFECTIVENESS ANALYSIS**<br><br>**Disease Specific Measures**<br>CRQ Total Score (€)<br><br>**Generic Measures**<br>QALYs gained (€) | **Incremental Cost Effectiveness Ratios**<br>(Difference in Mean Cost / Difference in Mean Effect)<br><br>850<br><br>472,000 | |
| **Probability that the Intervention is Cost Effective at Threshold Value (λ)** | | |
| **Threshold Value (λ)** | **CRQ Total** | **QALYs gained** |
| **λ = €5,000** | 0.980 | 0.000 |
| **λ = €15,000** | 0.992 | 0.001 |
| **λ = €25,000** | 0.994 | 0.001 |
| **λ = €35,000** | 0.994 | 0.003 |
| **λ = €45,000** | 0.994 | 0.007 |

**Note 1:** Incremental total costs estimated using GEE models assuming Gamma variance function, identify link function, exchangeable correlation, and controlling for treatment arm, baseline value, clustering.
Incremental CRQ/QALYs estimated using GEE models assuming Gaussian variance function, identify link function, exchangeable correlation, and controlling for treatment arm, baseline value, and clustering.

**Note 2**: Probabilities for cost effectiveness estimated parametrically using net benefit regression models for analysis at each level of **λ.**

**Figure 1 - Cost Effectiveness Acceptability Curves**

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**Contributors**

Kathy Murphy, Dympna Casey, Declan Devane, Bernard McCarthy, Adeline Cooney, Lorraine Mee, Collete Kirwan conceived the study and together with John Newell and O'Shea participated in the design of the trial and intervention. Paddy Gillespie and Eamon O'Shea undertook the acquisition, analysis and interpretation of the health economic data and the drafting of the research article. All authors participated in critical revision of the manuscript, and have approved the final version.

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**Ethical approval**

Ethical approval has been granted by the Research Ethics Committee of the National University of Ireland, Galway and the Irish College of General Practitioners (ICGP).

**Competing Interests**

The authors report no competing interests. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: that a research grant from the Health Research Board, Ireland was received to undertake the study, and an unconditional Educational Grant was obtained from Pfizer which provided support services to cover desk-top publication costs for manuals, and support for spirometery. The funders had no part in the design of the study; the collection, analysis, and interpretation of the data; the writing of the report; and the decision to submit the article for publication. All authors declare that no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Data sharing**:

No additional data are available.

**Copyright**

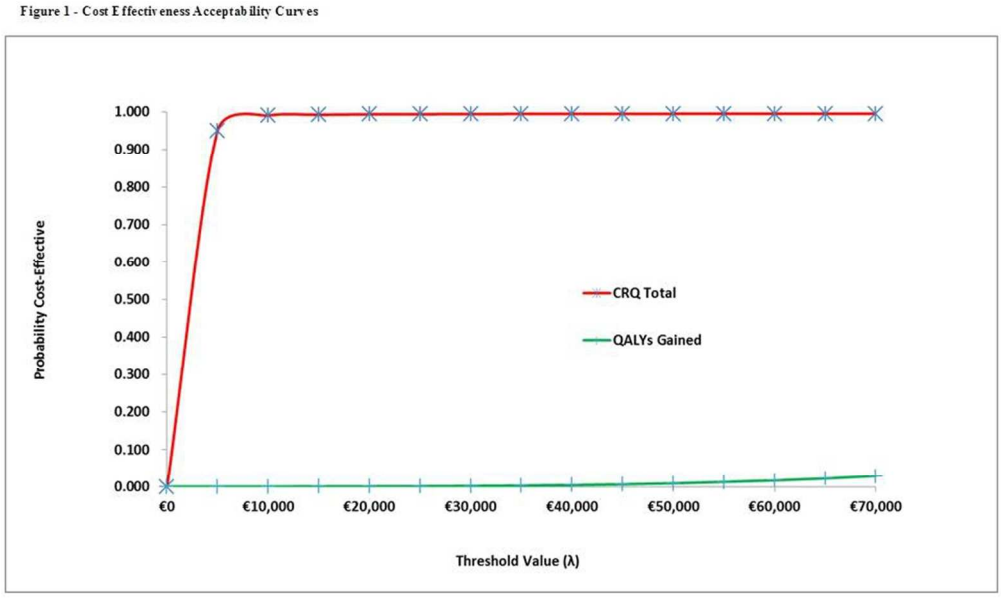


Figure 1: Cost Effectiveness Acceptability Curves
254x190mm (96 x 96 DPI)

**EVEREST Statement**: Checklist for Health Economics Paper:

**Title:** The cost effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial.

| | **Study section** | **Additional remarks** |
|---|---|---|
| **Study design** | | |
| (1) The research question is stated | In Abstract and in the Introduction (pg6) | |
| (2) The economic importance of the research question is stated | In the Introduction (pg 6) | |
| (3) The viewpoint(s) of the analysis are clearly stated and justified | In the Methods: Overview (pg6) | |
| (4) The rationale for choosing the alternative programmes or interventions compared is stated | In the Introduction (pg 5) | As the study is conducted alongside a trial – the alternatives were specified by the trial. |
| (5) The alternatives being compared are clearly described | In the Introduction (pg 5) | |
| (6) The form of economic evaluation used is stated | In the Introduction (pg 5), and in the Methods (pg 7) | We present both CEA and CUA as we use two outcome measures. |
| (7) The choice of form of economic evaluation is justified in relation to the questions addressed | We justify the methods used in the Introduction (pg 6) and the Discussion (10-12) | . |
| | | |
| **Data collection** | | |
| (8) The source(s) of effectiveness estimates used are stated | In the Methods (pg 6-9) | |
| (9) Details of the design and results of effectiveness study are given (if based on single study) | In the Introduction (pg 5-6) and in the Methods (pg 6-9) | |
| (10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies) | N/A | The analysis is based on a single trial |
| (11) The primary outcome measure(s) for the economic evaluation are clearly stated | In the Methods (pg 6-9) | |
| (12) Methods to value health states and other benefits are stated | In the Methods (pg 6-9) | |
| (13) Details of the subjects from whom valuations were obtained are given | In the Methods (pg 6-9) | |

| | | |
|---|---|---|
| (14) Productivity changes (if included) are reported separately | N/A | |
| (15) The relevance of productivity changes to the study question is discussed | N/A | |
| (16) Quantities of resources are reported separately from their unit costs | In Table 2 | |
| (17) Methods for the estimation of quantities and unit costs are described | In the Methods (pg 6-9) and in Table 1 | |
| (18) Currency and price data are recorded | In the Methods (pg6-9) and in Tables 1-3 | |
| (19) Details of currency of price adjustments for inflation or currency conversion are given | In the Methods (pg 6-9) | |
| (20) Details of any model used are given | N/A | |
| (21) The choice of model used and the key parameters on which it is based are justified | N/A | |
| | | |
| **Analysis and interpretation of results** | | |
| **(**22) Time horizon of costs and benefits is stated | In the Methods (pg 6) | Based on the follow up of the trial |
| (23) The discount rate(s) is stated | N/A | Given the length of follow up in the trial |
| (24) The choice of rate(s) is justified | N/A | |
| (25) An explanation is given if costs or benefits are not discounted | N/A | |
| (26) Details of statistical tests and confidence intervals are given for stochastic data | In the Results (pg 9-10) and in Table 3 | |
| (27) The approach to sensitivity analysis is given | In the Methods (pg 8-9) and in Table 3 and Figure 1. | CEACs |
| (28) The choice of variables for sensitivity analysis is justified | N/A | |
| (29) The ranges over which the variables are varied are stated | N/A | |
| (30) Relevant alternatives are compared | In the Results (pg 9-10) and in Table 3 and Figure 1 | |
| (31) Incremental analysis is reported | In the Results (pg 9-10) and in Table 3 and Figure 1 | |
| (32) Major outcomes are presented in a disaggregated as well as aggregated form | In Tables 2 and 3 | |
| (33) The answer to the study question is given | In the Discussion (pg 10-12) | |
| (34) Conclusions follow from the data reported | In the Discussion (pg 10-12) | |

| | | |
|---|---|---|
| (35) Conclusions are accompanied by the appropriate caveats | In the Discussion (pg 10-12) | |

BMJ open

# The cost effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial.



| | |
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**COVER SHEET**

**Title**: The cost effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial.

**Short Title:** The PRINCE Study: Cost Effectiveness Analysis

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## ARTICLE SUMMARY

### Article focus

- Pulmonary rehabilitation is a key strategy in the clinical management of chronic obstructive pulmonary disease.
- Little is known about the cost effectiveness of pulmonary rehabilitation for chronic obstructive pulmonary disease delivered in primary care.

### Key messages

- There is disease-specific evidence for the cost effectiveness of a structured education programme for chronic obstructive pulmonary disease delivered in primary care.
- Results depend on whether disease-specific or generic measures of health status are used to judge effectiveness: there was favourable evidence for the former; while no such evidence existed for the latter.
- It is important to calculate incremental cost effectiveness results for both disease-specific and generic outcome measures when conducting economic evaluation of interventions for chronic obstructive pulmonary disease.

### Strengths and Limitations

- Strengths include the study design, the sample size, and the range of resource, cost and economic patient level data collected for analysis.
- Limitations include the time horizon of the analysis which was confined to the trial follow up period, thereby reducing the ability to gauge the longer term effects of treatment.

## ABSTRACT

**Objective:**

To assess the cost effectiveness of a structured education pulmonary rehabilitation programme (SEPRP) for chronic obstructive pulmonary disease (COPD) relative to usual practice in primary care. The programme consisted of one group-based session per week over eight weeks delivered jointly by practice nurses and physiotherapists.

**Design:**

Economic evaluation, employing cost effectiveness and cost utility analysis, alongside a cluster randomised controlled trial.

**Setting:**

32 general practice surgeries in Ireland

**Participants:**

350 adults with COPD, 69% of whom are moderately affected.

**Interventions:**

Intervention arm (n=178) received a two-hour group-based SEPRP session per week over eight weeks delivered jointly by a practice nurse and physiotherapist at the practice surgery or nearby venue. Control arm (n=172) received usual practice in primary care.

**Main Outcome Measures:**

Incremental costs, Chronic Respiratory Questionnaire (CRQ), quality adjusted life years (QALYs) gained estimated using the generic EQ5D instrument, and expected cost effectiveness at 22 weeks trial follow up.

**Results:**

The intervention was associated with an increase of €944 (95% CIs: 489, 1400) in mean healthcare cost and €261 (95% CIs: 226, 296) in mean patient cost. The intervention was associated with a mean improvement of 1.11 (95% CIs: 0.35, 1.87) in CRQ Total score and 0.002 (95% CIs: -0.006, 0.011) in QALYs gained. These translated into incremental cost effectiveness ratios of €850 per unit increase in CRQ Total score and €472,000 per additional QALY gained. The probability of the intervention being cost effective at respective threshold values of €5,000, €15,000, €25,000 €35,000, and €45,000 was 0.980, 0.992, 0.994, 0.994, and

0.994 in the CRQ Total score analysis compared to 0.000, 0.001, 0.001, 0.003, and 0.007 in the QALYs gained analysis.

**Conclusions:**

While favourable cost effectiveness results exist when health status was measured using the disease-specific CRQ instrument, no evidence exists when effectiveness was measured in QALYS gained.

**KEY WORDS**:

COPD; Pulmonary Rehabilitation; Structured Education; Cost Effectiveness

**TRIAL REGISTRATION:**

Current Controlled Trials ISRCTN52403063

## INTRODUCTION

Pulmonary rehabilitation is key strategy in the clinical management of chronic obstructive pulmonary disease (COPD) and has been shown to be effective in improving patients' health related quality of life.[1, 2, 3] While much of the established evidence relates to programmes delivered in hospital, outpatient, or home settings,[4,5] there are growing calls for the provision of such services in the primary care setting.[6,7] Nonetheless, further evidence on clinical and cost effectiveness is required before primary care provision can be recommended. The PRINCE study sought to examine the clinical and cost effectiveness of pulmonary rehabilitation for COPD delivered at the level of general practice in Ireland.[8] To this end, the study evaluated a structured education pulmonary rehabilitation programme (SEPRP) intervention based on evidence collected alongside the cluster randomized controlled trial (RCT).[8]. The SEPRP consisted of a two-hour group-based session each week for eight weeks delivered jointly by practice nurses and physiotherapists and was compared in the trial to usual practice in primary care. The primary outcome in the clinical analysis was change in disease-specific health status from baseline to follow up, as measured using the Chronic Respiratory Questionnaire (CRQ) instrument,[9] with results indicating a significant improvement in health status for patients who received the intervention relative to the control of usual care.[10]

In addition to clinical effectiveness, any decision regarding the adoption of a healthcare intervention in clinical practice will depend upon its expected cost effectiveness.[11]The technique of economic evaluation compares the relative cost effectiveness of alternative treatment strategies by relating their mean differences in cost to their mean differences in effectiveness, and by quantifying the uncertainty surrounding these incremental point estimates. Central to this process is the selection of suitable outcome measures which enable the detection of clinically important treatment effects. In addition, and in order to more fully inform priority setting, generic outcome measures are preferable as they enable the comparison of a wide range of programmes across multiple patient populations, all of which may be competing for limited healthcare resources. Notably however, recent evidence has cast doubt on the ability of generic outcome measures to adequately capture meaningful differences in clinical severity for COPD patient populations.[12] Indeed, the adoption of generic rather than disease-specific measures in this context may lead to the underestimation of treatment benefits, biased cost effectiveness results, and ill-informed policy decisions.[13]

With this in mind, we present and compare cost effectiveness and cost utility results for disease-specific health status, as measured by the CRQ, and generic health status, as measured by quality adjusted life years (QALYs) gained.

## METHODS

### The PRINCE Cluster RCT

Full details of the study methods are published elsewhere.[8] In brief, a cluster randomized controlled trial (RCT) recruited 32 general practices and 350 patients with a diagnosis of COPD as defined by the GOLD guidelines.[14] Ethical approval was provided by the local ethics committees at the participating study centres. Practices were randomised to the control group, where patients (n=172) received usual care in general practice, or the intervention group, in which patients (n=178) received a structured education pulmonary rehabilitation programme (SEPRP). The SEPRP consisted of an eight-week programme with a group two-hour session each week delivered jointly by a practice nurse and physiotherapist at the practice surgery or nearby venue. The practice nurse facilitated the educational content of the programme and the physiotherapist focused on delivering the exercise component. The practice nurse also provided on-going advice and support to participants as required throughout the intervention period. In addition, participants were followed-up formally via telephone call at 4 weeks after completion of the SEPRP and via a 1-hour group session at 10 weeks. To facilitate the delivery of the intervention, educators received training via specialised preparation programmes and on-going support from the research team. To ensure standardisation of programme content and delivery, all training was provided by research staff, and educators were audited to ensure adherence to programme principles and content.

Details on the characteristics of the study participants are presented in Appendix Table 1 and were broadly similar across treatment arms.[10] Two patients in the intervention group and 6 patients in the control group died over the course of the trial and are excluded from the analysis, leaving 342 (98%) for the statistical analysis.[10] The primary outcome in the clinical analysis was change in disease-specific health status from baseline to follow up, as measured using the CRQ.[9] At trial follow up, the intervention was associated with statistically significant improvements in CRQ Dyspnoea scores (0.49; 95% CIs: 0.20, 0.78), CRQ Physical scores (0.37; 95% CIs: 0.14, 0.60), and CRQ Total score (1.11; 95% CIs: 0.35,

1.87) relative to the control.[10] There were concerns, however, that the confidence intervals did not exclude differences in effect that were pre-specified as clinically insignificant.[10]

**Economic Evaluation**

The economic evaluation consisted of a trial-based analysis with a time horizon of 22 weeks, the trial follow up period. The perspective of the healthcare provider was adopted with respect to costing and health outcomes were expressed in terms of disease-specific and generic health status. Data are also presented for private patient expenses. Evidence on resource use and health status, specifically CRQ and EQ5D, was collected via structured questionnaires and practice note searches at baseline (for the 26 weeks pre-randomisation) and follow up. Given the length of follow up, neither nether costs nor outcomes were discounted. The statistical analysis was conducted on an intention to treat basis, and in accordance with current guidelines for clinical and cost effectiveness analysis alongside cluster RCTs.[15,16] That is, we adopt statistical techniques which recognise both the clustering and correlation of cost and effect data. The incremental analyses were undertaken using generalised estimating equations (GEE), a flexible multivariate regression framework that explicitly allows for the modelling of normal and non-normal distributional forms of clustered data.[17] Uncertainty in the analysis was addressed by estimating 95% confidence intervals and cost effectiveness acceptability curves, which link the probability of a treatment being cost effective to a range of potential threshold values ($\lambda$) that the health system may be willing to pay for an additional unit of effect.[11] In addition, sensitivity analysis was undertaken to examine the effect of conducting a complete case only analysis and of varying the cost of delivering the intervention in practice. All analysis was undertaken using STATA and EXCEL statistical packages.

**Cost Analysis**

Three cost components were included in the analysis, all of which were expressed in Euros (€) in 2009 prices. The first was the cost of implementing the intervention in clinical practice and included resources relating to: educator and patient recruitment; educator, administrator and patient time input; venue and equipment rental; educational materials and consumables; and post, packaging, telephone and travel expenses (see Appendix Table 2).These costs were allocated to all 178 patients who participated in the SEPRP intervention. In sensitivity analysis, we explore the effect to expanding the number of patients per SEPRP session from

an average of 11 to 15, or 240 in total, and 20, or 320 in total, respectively; thereby reducing the intervention cost per patient.

Second, costs relating to the use of primary and secondary healthcare services over the course of the trial were estimated. This included the costs of general practitioner (GP), practice nurse, physiotherapist, dietician, public health nurse, home help, and social worker consultations, outpatient services, accident and emergency (A&E) visits, hospital admissions, COPD medications and oxygen therapy. Third, private costs to patients, in terms of time input and travel expenses over the course of the trial, were included. Resource use was captured via a combination of chart searches and patient questionnaires conducted by research staff at baseline and follow up. A vector of unit costs was applied to calculate the cost associated with each resource activity at baseline and follow up (see Table 1). Unit cost estimates for each activity were based on national data sources and, where necessary, were transformed to Euros (€) in 2009 prices using appropriate indices.[18,19] In particular, unit costs per consultation were obtained from published health service documents while drugs were costed using the monthly index of medical specialties for Ireland.

Two total cost variables were constructed for the incremental analysis: (i) total healthcare cost and (ii) total patient cost. To facilitate this process, imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing values for individual resource use at follow up. While the amount of missing data was very low, we adopted this approach to ensure a more complete analysis. Estimation of incremental costs at follow up was undertaken using GEE regression models controlling for treatment arm, baseline cost, and clustering. To account for the non-normal nature of the cost data, multilevel regression models assuming a gamma variance function were estimated.[20]

**Effectiveness Analysis**

Health outcomes in the analysis were expressed in terms of disease-specific and generic measures of health status. COPD-specific health status was measured using the CRQ instrument,[9] which consists of 20 items which are subdivided into four domains: dyspnoea, fatigue, emotional function and mastery. The self-administered version of the CRQ with individualized dyspnea domain was used. Individuals were asked to rate each item on a 7-point scale from 1 (maximum impairment) to 7 (no impairment). Each domain is scored as the sum of the individual items.[9] Based on patient responses, three CRQ aggregate scores

can be calculated: (i) CRQ Physical, which is an aggregate of the dyspnoea and fatigue domains; (ii) CRQ Psychological, which is an aggregate of the emotional function and mastery domains; and (iii) CRQ Total, which is an aggregate of all four domains.[9] For the purposes of the economic evaluation, only the CRQ Total score variable was included in the incremental cost effectiveness analysis.

Generic health status was expressed in terms of QALYs gained calculated based on patient responses to the EuroQol EQ5D 3L instrument.[21,22] The EQ5D consists of five dimensions: mobility, self-care, usual activities, pain or discomfort and anxiety or depression; and each dimension has three levels of severity: no problems, moderate problems or extreme problems. EQ5D responses are transformed using an algorithm into a single health state index score, based on values elicited via the time trade-off approach for the UK population,[23,24] which typically range from 0 (equivalent to death) to 1 (equivalent to good health), although a small number of health states are valued as worse than death. EQ5D scores at baseline and follow up were used to calculate patient-specific QALYs gained over 22 weeks using the area under the curve method.[25] Once again, to facilitate this process, imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing values at follow up. Estimation of incremental effectiveness at follow up was undertaken using GEE regression models, assuming a Gaussian variance function, and controlling for treatment arm, baseline EQ5D score, and clustering.

**Cost Effectiveness Analysis**

To undertake the cost effectiveness analysis, we adopt techniques which recognise both the clustering and correlation of cost and effect data collected alongside cluster RCTs. In economic evaluation, one treatment is defined as more cost effective than its comparator if one of the following conditions apply: (a) it is less costly and more effective; (b) it is more costly and more effective, but its additional cost per additional unit of effect, known as the incremental cost effectiveness ratio (ICER), is considered worth paying by decision makers; or (c) it is less costly and less effective, but the additional cost per additional unit of effect of its comparator is not considered worth paying by decision makers.[11] We employ the net benefit framework,[26] which allows for costs and effectiveness, and their correlation, to be combined into a single variable for each individual, to identify which of these three conditions applies in this case.

We define net benefit (*nb*) as,

$nb_{ijk} = e_{ijk}\lambda - c_{ijk}$,

where $e_{ijk}$ is the health outcome for the $_i$th person in the $_j$th cluster in treatment arm $_k$, λ is the cost effectiveness threshold value, and $c_{ijk}$ is their cost. Using this framework, the intervention is defined to be cost effective, at a given threshold value, λ, if its corresponding net benefit is greater than that of the control: that is, if the incremental net benefit for the intervention minus control is greater than zero.

Net benefit statistics for CRQ Total score and QALYs gained were calculated by relating total healthcare costs to the outcome measures of interest for a series of threshold values (ranging from λ = €0 to €70,000). Imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing CRQ values at follow up. Estimation of incremental net benefit was undertaken using GEE regression models, assuming a Gaussian variance function, and controlling for treatment arm, baseline CRQ or EQ5D score, baseline healthcare cost and clustering. The incremental cost effectiveness results are presented using ICERs and cost effectiveness acceptability curves, which were estimated parametrically,[26] and report the probability that the intervention is more cost effective than the control. The curves incorporate the sampling uncertainty around the ICER estimates as well as the uncertainty around the true threshold value, λ,[27] which is not explicitly known for Ireland.[28]

## RESULTS

Raw data estimates for resource use, costs and health outcomes at follow up are summarised in Table 2 (for the equivalent baseline results see Appendix Table 3). The cost of the intervention was estimated at €822 per participant, which consisted of €564 in healthcare costs and €258 in patient costs (see Appendix Table 2). Individual resource costs were combined to calculate total costs of care and are presented in Table 3. In terms of total costs over 22 weeks follow up, the mean healthcare cost per patient in the control arm was €1505 (SD: 1872) and €2357 (SD: 3532) in the intervention arm. The equivalent results for total patient cost were €129 (SD: 113) and €380 (SD: 111) respectively.

In terms of disease-specific health status, mean CRQ Total score per patient at follow up was 19.10 (SD: 4.83) in the control arm and 20.82 (SD: 3.88) in the intervention arm (see Table 3). Further results for CRQ domain scores are presented in Table 2 and in Casey et al.[10] In terms of generic health status, mean QALYs gained per patient at 22 weeks was 0.305 (SD: 0.106) in the control arm and 0.337 (SD: 0.081) in the intervention arm (see Table 3).

The results from the incremental analyses are also presented in Table 3. These indicate that the intervention was, on average, associated with higher costs and improved health outcomes, as measured using the CRQ and QALYs, when compared to the control. The intervention was estimated to result in a statistically significant increase in mean cost per patient of €944 (95% CIs: 489, 1400; p<0.01) in total healthcare costs and €261 (95% CIs: 226, 296; p<0.01) in total patient costs. In respect of effectiveness, the intervention was associated with a statistically significant increase in mean CRQ Total score of 1.11 (95% CIs: 0.35, 1.87; p<0.01) per patient and a non-significant increase in mean QALYs gained of 0.002 (95% CIs: -0.006, 0.011; p=0.63) per patient.

These results translated into incremental cost effectiveness ratios of €850 per unit increase in CRQ Total score and €472,000 per additional QALY gained. In terms of expected cost effectiveness, the probabilistic results are summarised in Table 3 and presented graphically in Figure 1. These indicate that for the CRQ Total score analysis, the probability of the intervention being more cost effective than the control was 0.980, 0.992, 0.994, 0.994, and 0.994 at threshold values of €5,000, €15,000, €25,000 €35,000, and €45,000 respectively. For the QALYs gained analysis, the equivalent probability estimates were 0.000, 0.001, 0.001, 0.003, and 0.007 respectively. The results from the sensitivity analysis are presented in the appendix and generally conform to the expected cost effectiveness results reported for the primary analysis.

## DISCUSSION

On the basis of evidence collected alongside a cluster RCT, a structured education pulmonary rehabilitation programme for COPD delivered in primary care was, on average, more costly and more effective than usual general practice care. Notably however, while the intervention was associated with statistically significant improvements in disease-specific health status, this was not reflected in generic health status. Moreover, the confidence intervals for the

disease-specific analysis included differences in effect that were deemed clinically insignificant.[10] Given the uncertainty relating to the effectiveness data, there is unsurprisingly conflicting evidence regarding the value for money of the programme. While there is favourable cost effectiveness evidence when outcomes are measured in terms of disease-specific health status, no such evidence exists in relation to generic health status. More specifically, in the cost per CRQ Total score analysis, the probability that the intervention was more cost effective than usual care was 0.980 or greater for a range of potential threshold values, notwithstanding concerns relating to clinical insignificance. In stark contrast, the cost per QALY gained analysis indicates that the intervention is highly unlikely to be deemed cost effective relative to usual care or indeed other programmes inside and outside of COPD medicine.

The ceiling ratios per QALY gained presented provide a useful range for comparison, given the lack of an implicit or explicit values for Ireland, and the current weak evidence base with respect to this type of health economic analysis for Ireland. However, the approach we used in applying the same ceiling rates per unit increase in CRQ gained is problematic as these values may, or may not, be much lower than those presented. In comparison to countries such as the UK, the range of ceiling ratios presented may be too high for CRQ in particular, and it might have been more useful, if somewhat more cumbersome, to present a different range of ceiling ratios for each of the two outcomes. For example, the shape of the CEAC for CRQ would also likely be different if additional points between €0 and €5,000 were evaluated. The difficulty is that in the absence of evidence in regard to an appropriate range of ceiling ratios any decision will appear arbitrary and be open to criticism. As usual, it will ultimately be the responsibility of the relevant policy decision maker to determine whether the evidence presented is sufficient to justify the adoption of the SEPRP intervention in clinical practice. What is clear is that there were significant improvements in CRQ after adjusting for differences in baseline values between intervention and control groups.

This study highlights the complexity of resource allocation decision making in this context as variations in estimated incremental effectiveness have markedly different implications for policy depending on the specificity of the outcome. Indeed, the central question is whether our findings reflect an absence of a clinically significant treatment effect or alternatively a lack of sensitivity in the ability of the generic EQ5D instrument to detect a clinically meaningful improvement in COPD health status. In the case of the former, it is worth noting

that in contrast to the majority of trials included in a Cochrane systematic review,[4] most of the participants in our study had moderate COPD (FEV1 around 55-60% predicted).[10] This is not surprising given that the target COPD population in a primary care setting is, by definition, likely to be less severely affected than hospital-based populations. Overall, our results highlight the need for a better understanding of the relationship between COPD disease-specific and generic outcome measures, the importance of exploring cost effectiveness in terms of both disease-specific and generic health status for this patient population, and the need to consider both measures in the resource allocation decision making process. Indeed, our findings can be added to those of existing studies which explore how the adoption of generic rather than disease-specific measures in this context may lead to the underestimation of treatment benefits, biased cost effectiveness results, and ill-informed policy decisions.[12,13] Moreover, this study highlights the difficulty of identifying an appropriate ceiling ratio and drawing conclusions based on ICERs using non-preference-based measures.

That said, our study adds to the existing literature on the cost effectiveness of pulmonary rehabilitation for COPD by evaluating a programme delivered in primary care. There is a broad literature showing that such programmes are cost effective in various hospital, outpatient and home settings [29-37]. Moreover, it also adds to the growing evidence of cost-effectiveness gains from rehabilitation and self-management programmes delivered in primary care settings for other diseases such as diabetes [38,39] and heart disease.[40] Keeping people out of hospital has been shown to be the key driver in lowering costs in the majority of these studies. Moreover, those studies which have reported cost savings generally adopted time horizons for analysis of one year or more, while we were restricted to a follow up of only 22 weeks. The short-time horizon for our study is, therefore, a significant weakness to exploring the sustainability of the intervention. Extending the time horizon would likely improve the cost-effectiveness of the intervention, linked to lower hospital admissions, if the evidence of other studies can be used as a guide to future resource use in Ireland. It should also be noted that the use of 2009 prices in the analysis may have inflated costs. Medical inflation has fallen in the period since then, which would also likely contribute to an improvement in the cost effectiveness results into the future.

A few other points should be noted as having potential effects on the results of this study. The conduct of economic evaluation in Ireland is complicated by a paucity of relevant data. In

particular, given the lack of utility data the EQ5D instrument was adopted and assumed to be relevant for an Irish population. This may not be the case. The process of conducting cost analysis in Ireland is also compromised by the lack of nationally available unit cost data. In estimating unit costs for individual resource activities, we endeavoured at all times to be conservative in any assumptions adopted. Furthermore, while we employ an appropriate multilevel net benefit regression approach to account for the correlation and clustering in the cost and effect data, arguments could be made for alternative bivariate or non-parametric approaches.[16]

In conclusion, the evidence is contradictory in regard to the cost effectiveness of a structured education programme for COPD delivered in primary care in Ireland. While there appears to be favourable evidence in terms of disease-specific COPD health status, there is no such evidence in relation to generic health status as measured by QALYs. As a result, uncertainty surrounds the policy implications of this analysis. Nonetheless, the study confirms the importance of calculating incremental cost effectiveness results for both disease-specific and generic outcome measures for COPD patient populations.

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**Table 1 – Categories of Resource Use and Unit Cost Estimates in 2009 (€) Prices**

| RESOURCE ITEM | ACTIVITY | UNIT COST €'s | SOURCE |
|---|---|---|---|
| **Healthcare Resources** | | | |
| General Practitioner Visit | Per Consultation | 50 | ORC |
| Practice Nurse Visit | Per Consultation | 12 | DOHC |
| Hospital Admission Visit | Per Inpatient Day | 832 | DOHC |
| Outpatient Clinic Visit | Per Visit | 169 | DOHC |
| Accident and Emergency Clinic Visit | Per Visit | 289 | DOHC |
| Physiotherapist Visit | Per Consultation | 24 | HSE |
| Dietician Visit | Per Consultation | 24 | HSE |
| Public Health Nurse Visit | Per Consultation | 27 | HSE |
| Home Help Visit | Per Consultation | 16 | HSE |
| Social Worker Visit | Per Consultation | 24 | HSE |
| Spiriva (Tiotropium Bromide) | Per Day | 1.42 | MIMS |
| Seretide (Salmeterol, Fluticasone propionate) | Per Day | 2.22 | MIMS |
| Serevent (Salmeterol xinafoate) | Per Day | 0.94 | MIMS |
| Ventolin (Salbutamol Sulfate, Salamol) | Per Day | 0.24 | MIMS |
| Combivent (Ipratropium Bromide-Salbutamol Sulfate) | Per Day | 0.83 | MIMS |
| Singulair (Montelukast) | Per Day | 1.18 | MIMS |
| Becotide (Beclometasone, Beclazone) | Per Day | 0.27 | MIMS |
| Symbicort (Cortisone Inhalers) | Per Day | 1.55 | MIMS |
| Pulmicort (Budesonide) | Per Day | 0.82 | MIMS |
| Bricanyl (Terbutaline Sulfate) | Per Day | 0.21 | MIMS |
| Oral Prednisone (Prednesol, Deltacortril) | Per Day | 0.47 | MIMS |
| Oral Phyollocntin (Aminophylline) | Per Day | 0.28 | MIMS |
| Uniphyl (Theophylline) | Per Day | 0.19 | MIMS |
| Atrovent (Ipratropium bromide) | Per Day | 0.20 | MIMS |
| Oxygen Cylinder | Per Day | 4.91 | Britton et al, 2003 |
| Oxygen Concentrator | Per Day | 2.19 | Britton et al, 2003 |
| | | | |
| **Patient Resources** | | | |
| *Travel Expenses* | | | |
| Car | Per Mile | 1.06 | DOF |
| Bus | Per Mile | 1.64 | Dublin Bus |
| Taxi | Per Fare/Add. Mile | 3.71/1.56 | www.taxi.ie |
| *Time Input* | | | |
| Economically Active | Per Hour | 19 | CSO |
| Economically Inactive | Per Hour | 9 | CSO |

**Note:**
ORC – Office of the Revenue Commissioner, Dublin, Ireland.
DOHC – Casemix Unit, Department of Health and Children, Dublin, Ireland
HSE – Salary Scales, Health Service Executive, Dublin, Ireland
MIMS - Monthly Index of Medical Specialties Ireland, Dublin, Ireland
DOF – Department of Finance, Dublin, Ireland
CSO – Central Statistics Office, Dublin, Ireland

**Table 2 – Raw Data Estimates for Resource Use, Costs and Health Outcomes at 22 Weeks Follow Up**

| VARIABLE | INTEVENTION (N=178) *Mean (SD) / %* | | CONTROL (N=172) *Mean (SD) / %* | |
|---|---|---|---|---|
| **RESOURCE ITEM** | **Usage** | **Cost (€)** | **Usage** | **Cost(€)** |
| **Healthcare Resources** | | | | |
| GP Visits: Breathing Problems | 1.6 (2.0) | 134 (122) | 1.8 (2.5) | 153 (158) |
| GP Visits: Other | 2.4 (2.5) | 118 (124) | 2.7 (2.7) | 133 (136) |
| Practice Nurse Visits: Breathing Problems | 0.1 (0.3) | 1 (4) | 0.1 (0.5) | 2 (6) |
| Practice Nurse Visits: Other | 1.1 (2.0) | 13 (24) | 1.2 (2.1) | 14 (25) |
| Inpatient Days: Breathing Problems | 0.5 (2.8) | 411 (2300) | 0.1 (0.6) | 80 (504) |
| Inpatient Days: Other | 0.4 (2.5) | 336 (2054) | 0.3 (1.9) | 266 (1552) |
| Outpatient Visits: Breathing Problems | 0.2 (0.5) | 36 (90) | 0.3 (0.7) | 52 (124) |
| Outpatient Visits: Other | 0.8 (1.5) | 134 (253) | 0.7 (1.2) | 118 (208) |
| Accident &Emergency Visits: Breathing Problems | 0.1 (0.2) | 12 (57) | 0.1 (0.3) | 17 (76) |
| Accident &Emergency Visits: Other | 0.1 (0.3) | 23 (78) | 0.1 (0.2) | 16 (66) |
| Physiotherapist Visits: Breathing Problems | 0.3 (1.4) | 6 (33) | 0.2 (1.3) | 5 (30) |
| Physiotherapist Visits: Other | 0.5 (1.9) | 11 (46) | 0.5 (1.9) | 11 (45) |
| Public Health Nurse Visits: Breathing Problems | 0.1 (1.0) | 3 (27) | 0.1 (1.0) | 3 (28) |
| Public Health Nurse Visits: Other | 0.3 (1.6) | 8 (42) | 0.4 (1.9) | 12 (51) |
| Dietician Visits | 0.0 (0.2) | 1(4) | 0.0 (0.3) | 1 (6) |
| Home Help Visits | 3.9 (17.5) | 63(280) | 5.4 (20.3) | 87 (325) |
| Social Worker Visits | 0.0 (0.0) | 0 (0) | 0.0 (0.1) | 1 (2) |
| Spiriva | 59% | 138 (115) | 62% | 144 (113) |
| Seretide | 56% | 203 (182) | 55% | 200 (182) |
| Serevent | 1% | 2 (16) | 1% | 1 (12) |
| Ventolin | 53% | 21 (20) | 52% | 20 (20) |
| Combivent | 13% | 18 (46) | 15% | 21 (49) |
| Singulair | 9% | 16 (53) | 11% | 21 (60) |
| Becotide | 4% | 2 (9) | 7% | 3 (11) |
| Symbicort | 18% | 45 (97) | 20% | 50 (102) |
| Pulmicort | 4% | 5 (26) | 5% | 7 (30) |
| Bricanyl | 2% | 1 (5) | 2% | 1 (5) |
| Oral Prednisone | 4% | 3 (15) | 11% | 8 (24) |
| Oral Phyollocntin | 1% | 1 (4) | 3% | 1 (8) |
| Uniphyl | 8% | 3 (8) | 7% | 2 (8) |
| Atrovent | 7% | 2 (8) | 8% | 3 (9) |
| Oxygen Therapy | 3% | 16 (96) | 5% | 26 (121) |
| Intervention | n/a | 564 (n/a) | n/a | 0 (n/a) |
| **Patient Resources** | | | | |
| Travel Expenses | n/a | 88 (89) | n/a | 86 (80) |
| Time Input | n/a | 37 (32) | n/a | 39 (32) |
| Intervention | n/a | 258 (n/a) | n/a | 0 (n/a) |
| **HEALTH OUTCOME** | | | | |
| **Disease Specific Measure** | | | | |
| CRQ Dyspnea Score | 4.42 (1.36) | | 3.85 (1.45) | |
| CRQ Fatigue Score | 4.79 (1.31) | | 4.33 (1.47) | |
| CRQ Emotional Score | 5.62 (1.19) | | 5.24 (1.30) | |
| CRQ Mastery Score | 5.94 (1.11) | | 5.59 (1.30) | |
| CRQ Physical Score | 4.62 (1.10) | | 4.12 (1.29) | |
| CRQ Psychological Score | 5.78 (1.06) | | 5.41 (1.22) | |
| **Generic Measure** | | | | |
| EQ5D Score at Follow up | 0.801 (0.232) | | 0.762 (0.252) | |

**Note:** Eight patients (6 intervention and 2 control) who died over the course of the study were excluded from the analysis. Completeness of cost data: ***Intervention*** - 99% for on primary care utilisation, 99% for secondary care utilisation, 80% for community care utilisation, 99% for medication utilisation, 80% for oxygen therapy utilisation, and 78% for Total Healthcare Cost. ***Control***: 97% 97%, 78%, 97%, 78% and 78% respectively. Completeness of effect data: ***Intervention*** - 80% for CRQ, 80% for EQ5D and 80% for QALY scores. ***Control*** - 78%, 78% and 78% (N=134) respectively.

**Table 3 – Incremental Cost Effectiveness Results**

| **COST ANALYSIS** | **INTEVENTION (N=178)** *Mean (SD)* | **CONTROL (N=172)** *Mean (SD)* |
|---|---|---|
| **Healthcare Resources** Total Healthcare Cost per patient (€) | 2357 (3532) | 1505 (1872) |
| **Patient Resources** Total Patient Cost per patient (€) | 380 (111) | 129 (113) |
| | **Incremental Analysis** **Difference in Means (95% CI's) [p-value]** (Intervention versus Control) | |
| **Healthcare Resources** Total Healthcare Cost per patient (€) | 944 (489, 1400) [<0.01] | |
| **Patient Resources** Total Patient Cost per patient (€) | 261 (226, 296) [<0.01] | |
| | | |
| **EFFECTIVENESS ANALYSIS** | **INTEVENTION (N=178)** *Mean (SD)* | **CONTROL (N=172)** *Mean (SD)* |
| **Disease Specific Measures** CRQ Total Score | 20.82 (3.88) | 19.10 (4.83) |
| **Generic Measures** QALYs gained | 0.337 (0.081) | 0.305 (0.106) |
| | **Incremental Analysis** **Difference in Means (95% CI's)[p-value]** (Intervention versus Control) | |
| **Disease Specific Measures** CRQ Total Score | 1.11 (0.35, 1.87) [<0.01] | |
| **Generic Measures** QALYs gained | 0.002 (-0.006, 0.011) [0.63] | |
| | | |
| **COST EFFECTIVENESS ANALYSIS** | **Incremental Cost Effectiveness Ratios** (Difference in Mean Cost / Difference in Mean Effect) | |
| **Disease Specific Measures** Cost per CRQ Total Score (€) | 850 | |
| **Generic Measures** Cost per QALYs gained (€) | 472,000 | |

**Probability that the Intervention is Cost Effective at Threshold Value (λ)**

| **Threshold Value (λ)** | **CRQ Total** | **QALYs gained** |
|---|---|---|
| **λ = €5,000** | 0.980 | 0.000 |
| **λ = €15,000** | 0.992 | 0.001 |
| **λ = €25,000** | 0.994 | 0.001 |
| **λ = €35,000** | 0.994 | 0.003 |
| **λ = €45,000** | 0.994 | 0.007 |

**Note 1:** Incremental total costs estimated using GEE models assuming Gamma variance function, identify link function, exchangeable correlation, and controlling for treatment arm, baseline value, clustering. Incremental CRQ/QALYs estimated using GEE models assuming Gaussian variance function, identify link function, exchangeable correlation, and controlling for treatment arm, baseline value, and clustering.

**Note 2**: Probabilities for cost effectiveness estimated parametrically using net benefit regression models for analysis at each level of **λ.**

**Figure 1 - Cost Effectiveness Acceptability Curves**

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**Contributors**

Kathy Murphy, Dympna Casey, Declan Devane, Bernard McCarthy, Adeline Cooney, Lorraine Mee, Collete Kirwan conceived the study and together with John Newell and O'Shea participated in the design of the trial and intervention. Paddy Gillespie and Eamon O'Shea undertook the acquisition, analysis and interpretation of the health economic data and the drafting of the research article. All authors participated in critical revision of the manuscript, and have approved the final version.

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**Ethical approval**

Ethical approval has been granted by the Research Ethics Committee of the National University of Ireland, Galway and the Irish College of General Practitioners (ICGP).

**Competing Interests**

The authors report no competing interests. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: that a research grant from the Health Research Board, Ireland was received to undertake the study, and an unconditional Educational Grant was obtained from Pfizer which provided support services to cover desk-top publication costs for manuals, and support for spirometery. The funders had no part in the design of the study; the collection, analysis, and interpretation of the data; the writing of the report; and the decision to submit the article for publication. All authors declare that no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Data sharing**:

No additional data are available.

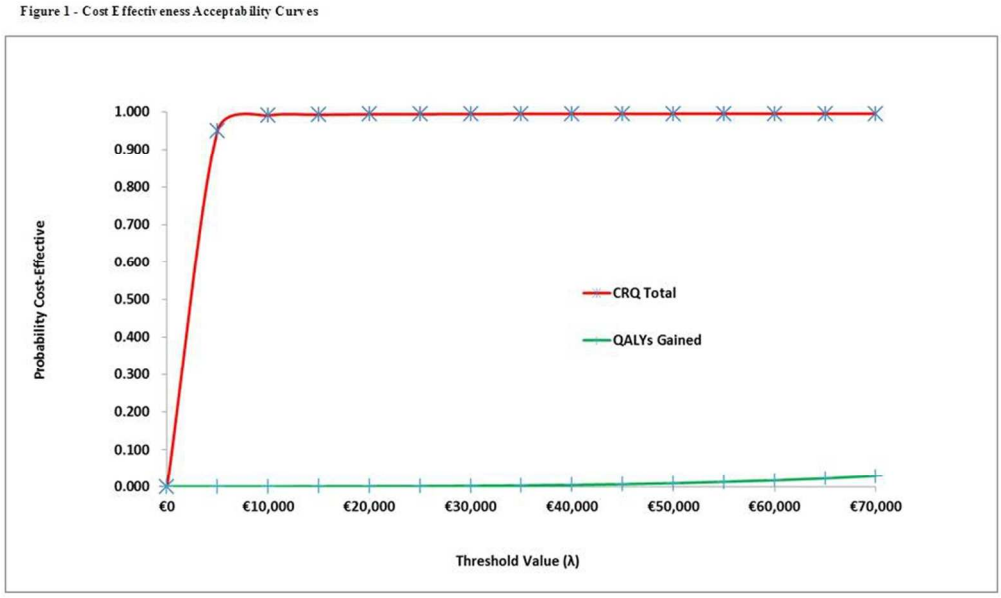


Figure 1: Cost Effectiveness Acceptability Curves
254x190mm (96 x 96 DPI)

**Appendix Table 1 - Characteristics of clusters (general practices) and baseline demographic and clinical characteristics of COPD patients assigned to intervention (SEPRP) or continued usual care. Values are numbers (percentages) unless stated otherwise (Casey et al, 2013)**

**Comment [i1]:** We now explicitly reference the clinical paper from which this table is obtained with permission.

| Characteristics | Intervention (n=178) | Control (n=172) |
|---|---|---|
| No of clusters* | 16 | 16 |
| Median (range) of participants per cluster | 11 (8-14) | 10 (9-14) |
| GP Practice (cluster) | | |
| Urban | 32 (18.0) | 61 (35.5) |
| Rural | 146 (82.0) | 111 (64.5) |
| < 5,000 patients | 88 (49.4) | 64 (37.2) |
| > 5,000 patients | 90 (50.6) | 108 (62.8) |
| Mean (SD) age (years) | 68.8 (10.2) | 68.4 (10.3) |
| Gender | | |
| Male (n, %) | 117 (65.7) | 106 (61.6) |
| Female (n, %) | 61 (34.3) | 66 (38.4) |
| Marital status: | | |
| Married/Living with partner | 111 (62.4) | 115 (66.9) |
| Separated /Divorced | 15 (8.4) | 10 (5.8) |
| Widowed | 26 (14.6) | 21 (12.2) |
| Single / Never married | 26 (14.6) | 26 (15.1) |
| Medical Card Holder | 141 (79.2) | 152 (88.4) |
| Employment status: | | |
| Paid Work: Employee | 17 (9.6) | 12 (7.0) |
| Paid Work: Self employed | 14 (7.9) | 8 (4.7) |
| Homemaker | 26 (14.6) | 19 (11.0) |
| Unemployed looking for work | 8 (4.5) | 8 (4.7) |
| Retired- | 92 (51.7) | 111 (64.5) |
| Unable to work disability | 16 (9.0) | 9 (5.2) |
| Other | 5 (2.8) | 5 (2.9) |
| Spirometry (post-bronchodilator): | | |
| FEV1(% Predicted) [mean (SD)] | 57.6 (14.3) | 59.7 (13.8) |
| FEV1/FVC [mean (SD)] | 52.9 (11.5) | 55.4 (11.9) |
| • GOLD 3 Severe COPD** n=97 (27.7%) | 56 (31.5%) | 41 (23.8%) |
| • GOLD 2 Moderate COPD** n=253 (72.3%) | 122 (68.5%) | 131(76.2%) |
| Patient history (from medical records) | | |
| Hypertension or High Cholesterol | 66 (37.1) | 76 (44.2) |
| Cardiovascular disease | 41 (23.0) | 62 (36.0) |
| Muscoskeletal problems | 66 (37.1) | 73 (42.4) |
| Diabetes | 22 (12.4) | 28 (16.3) |
| Asthma | 38 (22.1) | 41 (23.0) |
| Gastrointestinal disorders | 43 (24.2) | 46 (26.7) |
| CNS Disorders | 18 (10.1) | 21 (12.2) |
| Mental health problems | 28 (15.7) | 27 (15.7) |
| Use of inhalers | 155 (87.1) | 158 (91.9) |
| Home oxygen | 6 (3.4) | 11 (6.4) |
| Never smoked | 16 (9.0) | 27 (15.7) |
| Current smoker (n, %) | 70 (39.3) | 59 (34.3) |
| • Males currently smoking (n, %) | 44 (37.6%) | 33 (31.1%) |
| • Females currently smoking (n, %) | 26 (42.6%) | 26 (39.4%) |

**Note:** * Clusters = GP Practice; ** Classification of COPD based on the GOLD criteria; SD = Standard Deviation

**Appendix Table 2 – Intervention Costs**

| Resource item | | Total Cost |
|---|---|---|
| **Physiotherapist and Practice Recruitment**<br><br>Research Team Time Input; Documentation; Phone Calls, Postage & Packaging | | €688 |
| **Physiotherapist Preparation Programme**<br><br>Research Team Time Input; Participant Time Input; Venue & Equipment Rental; Educational/Training Materials & Consumables; Travel Expenses; Documentation; Phone Calls, Postage & Packaging | | €8,691 |
| **Practice Nurse Preparation Programme**<br><br>Research Team Time Input; Participant Time Input; Venue & Equipment Rental; Educational/Training Materials & Consumables; Travel Expenses; Documentation; Phone Calls, Postage & Packaging | | €24,588 |
| **Patient Recruitment**<br><br>Research Team Time Input; Practice Nurse Time Input; Spirometry Tests, Documentation; Phone Calls, Postage & Packaging | | €11,942 |
| **SEPRP Intervention**<br><br>Physiotherapist and Practice Nurse Time Input; Research Team Time Input; Participant Time Input; Venue & Equipment Rental; Educational/Training Materials & Consumables; Travel Expenses; Documentation; Phone Calls, Postage & Packaging | | €100,483 |
| | | |
| **Total Cost** | | **€146,391** |
| **Total Cost Per Patient** (*n=178 patients*) | | **€822** |
| | **Total Healthcare Cost Per Patient** | **€564** |
| | **Total Private Patient Cost per Patient** | **€258** |

**Note:** Total Healthcare Cost Per Patient used for incremental cost effectiveness analysis

**Comment [i2]:** We change this table to present the information more clearly.

**Appendix Table 3 – Raw Data Estimates at Baseline (26 weeks pre randomisation) for Resource Use, Costs and Health Outcomes**

| VARIABLE | INTEVENTION (N=178) *Mean (SD) / %* | | CONTROL (N=172) *Mean (SD) / %* | |
|---|---|---|---|---|
| **RESOURCE ITEM** | **Usage** | **Cost (€)** | **Usage** | **Cost(€)** |
| **Healthcare Resources** | | | | |
| GP Visits: Breathing Problems | 1.6 (1.7) | 78 (87) | 1.9 (2.8) | 95 (138) |
| GP Visits: Other | 2.7 (2.5) | 135 (123) | 3.2 (3.4) | 159 (171) |
| Practice Nurse Visits: Breathing Problems | 0.3 (0.9) | 3 (11) | 0.2 (0.7) | 2 (8) |
| Practice Nurse Visits: Other | 1.2 (2.2) | 14 (27) | 1.1 (1.8) | 13 (22) |
| Inpatient Days: Breathing Problems | 0.3 (1.2) | 224 (999) | 0.3 (1.5) | 266 (1219) |
| Inpatient Days: Other | 0.7 (4.2) | 538 (3461) | 0.3 (1.3) | 247 (3461) |
| Outpatient Visits: Breathing Problems | 0.3 (0.5) | 44 (90) | 0.5 (1.0) | 90 (167) |
| Outpatient Visits: Other | 0.9 (1.4) | 147 (237) | 1.0 (1.7) | 166 (278) |
| Accident &Emergency Visits: Breathing Problems | 0.1 (0.2) | 13 (60) | 0.1 (0.4) | 29 (116) |
| Accident &Emergency Visits: Other | 0.1 (0.4) | 31 (113) | 0.1 (0.3) | 24 (91) |
| Physiotherapist Visits: Breathing Problems | 0.5 (2.3) | 13 (55) | 0.4 (2.0) | 10 (47) |
| Physiotherapist Visits: Other | 0.7 (2.5) | 16 (60) | 0.6 (2.4) | 15 (58) |
| Public Health Nurse Visits: Breathing Problems | 0.1 (0.4) | 2 (10) | 0.5 (2.1) | 13 (57) |
| Public Health Nurse Visits: Other | 0.4 (1.9) | 11 (52) | 0.7 (2.6) | 19 (69) |
| Dietician Visits | 1.0 (3.2) | 24 (77) | 0.1 (0.4) | 2 (9) |
| Home Help Visits | 5.4 (22.1) | 86 (354) | 7.8 (26.3) | 125 (420) |
| Social Worker Visits | 0.0 (0.1) | 1 (3) | 0.0 (0.1) | 1 (3) |
| Spiriva | 55% | 141 (129) | 62% | 161 (126) |
| Seretide | 49% | 201 (204) | 58% | 234 (201) |
| Serevent | 2% | 3 (22) | 1% | 1 (13) |
| Ventolin | 53% | 23 (22) | 51% | 22 (22) |
| Combivent | 14% | 21 (53) | 15% | 23 (55) |
| Singulair | 7% | 15 (54) | 9% | 19 (61) |
| Becotide | 7% | 3 (12) | 5% | 2 (10) |
| Symbicort | 17% | 49 (107) | 20% | 56 (113) |
| Pulmicort | 3% | 4 (25) | 3% | 4 (25) |
| Bricanyl | 1% | 1 (4) | 2% | 1 (5) |
| Oral Prednisone | 6% | 5 (21) | 9% | 8 (25) |
| Oral Phyollocntin | 1% | 1 (4) | 2% | 1 (7) |
| Uniphyl | 7% | 3 (9) | 7% | 2 (9) |
| Atrovent | 7% | 2 (9) | 6% | 2 (9) |
| Oxygen Therapy | 3% | 22 (118) | 6% | 31 (139) |
| | | | | |
| **Patient Resources** | | | | |
| Travel Expenses | n/a | 109 (93) | n/a | 128 (115) |
| Time Input | n/a | 48 (35) | n/a | 59 (50) |
| | | | | |
| **Total Healthcare Cost** | n/a | 1870 (3855) | n/a | 1850 (2140) |
| **Total Patient Cost** | n/a | 164 (129) | n/a | 181 (159) |
| **HEALTH OUTCOME** | | | | |
| **Disease Specific Measures** | | | | |
| CRQ Dyspnea Score | 3.74 (1.20) | | 3.45 (1.39) | |
| CRQ Fatigue Score | 4.33 (1.31) | | 4.05 (1.48) | |
| CRQ Emotional Score | 5.39 (1.22) | | 5.01 (1.34) | |
| CRQ Mastery Score | 5.42 (1.31) | | 5.25 (1.38) | |
| CRQ Physical Score | 4.09 (1.12) | | 3.77 (1.23) | |
| CRQ Psychological Score | 5.41 (1.16) | | 5.13 (1.26) | |
| **CRQ Total Score** | 19.03 (4.16) | | 17.80 (4.56) | |
| | | | | |
| **Generic Measures** | | | | |
| EQ5D Score | 0.789 (0.209) | | 0.694 (0.296) | |

**Note :** Completeness of cost data: ***Intervention*** - 100% for primary care utilisation, 100% for secondary care utilisation, 100% for community care utilisation, 100% for medication utilisation, and 100% for oxygen therapy utilisation. ***Control***: 100%, 74%, 100%, 100%, 100% and 100% respectively. **Note 1:** Completeness of effect data: ***Intervention*** 100% for CRQ and 100% for EQ5D scores. ***Control***: 100% and 100% respectively.

**Appendix Table 4 Sensitivity Analysis 1 - Complete Case Analysis**

Comment [i3]: We now include three sensitivity analyses.

| COST EFFECTIVENESS ANALYSIS | Incremental Cost Effectiveness Ratios (Difference in Mean Cost / Difference in Mean Effect) | |
|---|---|---|
| **Disease Specific Measures** Cost per CRQ Total Score (€) | 660 | |
| **Generic Measures** Cost per QALYs gained (€) | 871,000 | |
| **Probability that the Intervention is Cost Effective at Threshold Value (λ)** | | |
| **Threshold Value (λ)** | **CRQ Total** | **QALYs gained** |
| **λ = €5,000** | 0.981 | 0.000 |
| **λ = €15,000** | 0.992 | 0.000 |
| **λ = €25,000** | 0.994 | 0.000 |
| **λ = €35,000** | 0.994 | 0.000 |
| **λ = €45,000** | 0.995 | 0.001 |

**Appendix Table 5 Sensitivity Analysis 2 - Intervention Cost €418 (15 patients per session)**

| COST EFFECTIVENESS ANALYSIS | Incremental Cost Effectiveness Ratios (Difference in Mean Cost / Difference in Mean Effect) | |
|---|---|---|
| **Disease Specific Measures** Cost per CRQ Total Score (€) | 725 | |
| **Generic Measures** Cost per QALYs gained (€) | 402,500 | |
| **Probability that the Intervention is Cost Effective at Threshold Value (λ)** | | |
| **Threshold Value (λ)** | **CRQ Total** | **QALYs gained** |
| **λ = €5,000** | 0.983 | 0.001 |
| **λ = €15,000** | 0.993 | 0.001 |
| **λ = €25,000** | 0.994 | 0.003 |
| **λ = €35,000** | 0.994 | 0.006 |
| **λ = €45,000** | 0.995 | 0.012 |

**Appendix Table 6 Sensitivity Analysis 3 - Intervention Cost €313 (20 patients per session)**

| COST EFFECTIVENESS ANALYSIS | Incremental Cost Effectiveness Ratios (Difference in Mean Cost / Difference in Mean Effect) | |
|---|---|---|
| **Disease Specific Measures** Cost per CRQ Total Score (€) | 636 | |
| **Generic Measures** Cost per QALYs gained (€) | 353,000 | |
| **Probability that the Intervention is Cost Effective at Threshold Value (λ)** | | |
| **Threshold Value (λ)** | **CRQ Total** | **QALYs gained** |
| **λ = €5,000** | 0.985 | 0.002 |
| **λ = €15,000** | 0.993 | 0.004 |
| **λ = €25,000** | 0.994 | 0.007 |
| **λ = €35,000** | 0.994 | 0.013 |
| **λ = €45,000** | 0.995 | 0.024 |

**EVEREST Statement**: Checklist for Health Economics Paper:

**Title:** The cost effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial.

| | **Study section** | **Additional remarks** |
|---|---|---|
| **Study design** | | |
| (1) The research question is stated | In Abstract and in the Introduction (pg6) | |
| (2) The economic importance of the research question is stated | In the Introduction (pg 6) | |
| (3) The viewpoint(s) of the analysis are clearly stated and justified | In the Methods: Overview (pg6) | |
| (4) The rationale for choosing the alternative programmes or interventions compared is stated | In the Introduction (pg 5) | As the study is conducted alongside a trial – the alternatives were specified by the trial. |
| (5) The alternatives being compared are clearly described | In the Introduction (pg 5) | |
| (6) The form of economic evaluation used is stated | In the Introduction (pg 5), and in the Methods (pg 7) | We present both CEA and CUA as we use two outcome measures. |
| (7) The choice of form of economic evaluation is justified in relation to the questions addressed | We justify the methods used in the Introduction (pg 6) and the Discussion (10-12) | . |
| | | |
| **Data collection** | | |
| (8) The source(s) of effectiveness estimates used are stated | In the Methods (pg 6-9) | |
| (9) Details of the design and results of effectiveness study are given (if based on single study) | In the Introduction (pg 5-6) and in the Methods (pg 6-9) | |
| (10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies) | N/A | The analysis is based on a single trial |
| (11) The primary outcome measure(s) for the economic evaluation are clearly stated | In the Methods (pg 6-9) | |
| (12) Methods to value health states and other benefits are stated | In the Methods (pg 6-9) | |
| (13) Details of the subjects from whom valuations were obtained are given | In the Methods (pg 6-9) | |

| | | |
|---|---|---|
| (14) Productivity changes (if included) are reported separately | N/A | |
| (15) The relevance of productivity changes to the study question is discussed | N/A | |
| (16) Quantities of resources are reported separately from their unit costs | In Table 2 | |
| (17) Methods for the estimation of quantities and unit costs are described | In the Methods (pg 6-9) and in Table 1 | |
| (18) Currency and price data are recorded | In the Methods (pg6-9) and in Tables 1-3 | |
| (19) Details of currency of price adjustments for inflation or currency conversion are given | In the Methods (pg 6-9) | |
| (20) Details of any model used are given | N/A | |
| (21) The choice of model used and the key parameters on which it is based are justified | N/A | |
| | | |
| **Analysis and interpretation of results** | | |
| **(**22) Time horizon of costs and benefits is stated | In the Methods (pg 6) | Based on the follow up of the trial |
| (23) The discount rate(s) is stated | N/A | Given the length of follow up in the trial |
| (24) The choice of rate(s) is justified | N/A | |
| (25) An explanation is given if costs or benefits are not discounted | N/A | |
| (26) Details of statistical tests and confidence intervals are given for stochastic data | In the Results (pg 9-10) and in Table 3 | |
| (27) The approach to sensitivity analysis is given | In the Methods (pg 8-9) and in Table 3 and Figure 1. | CEACs |
| (28) The choice of variables for sensitivity analysis is justified | N/A | |
| (29) The ranges over which the variables are varied are stated | N/A | |
| (30) Relevant alternatives are compared | In the Results (pg 9-10) and in Table 3 and Figure 1 | |
| (31) Incremental analysis is reported | In the Results (pg 9-10) and in Table 3 and Figure 1 | |
| (32) Major outcomes are presented in a disaggregated as well as aggregated form | In Tables 2 and 3 | |
| (33) The answer to the study question is given | In the Discussion (pg 10-12) | |
| (34) Conclusions follow from the data reported | In the Discussion (pg 10-12) | |

| | | |
|---|---|---|
| (35) Conclusions are accompanied by the appropriate caveats | In the Discussion (pg 10-12) | |

**COVER SHEET**

**Title**: The cost effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial.

**Short Title:** The PRINCE Study: Cost Effectiveness Analysis

**Authors:** Gillespie P, O'Shea E, Casey D, Murphy K, Devane D, Cooney A, Mee L, Kirwan C, McCarthy B, Newell J.

for the PRINCE study team

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## ARTICLE SUMMARY

### Article focus

- Pulmonary rehabilitation is a key strategy in the clinical management of chronic obstructive pulmonary disease.
- Little is known about the cost effectiveness of pulmonary rehabilitation for chronic obstructive pulmonary disease delivered in primary care.

### Key messages

- There is disease-specific evidence for the cost effectiveness of a structured education programme for chronic obstructive pulmonary disease delivered in primary care.
- Results depend on whether disease-specific or generic measures of health status are used to judge effectiveness: there was favourable evidence for the former; while no such evidence existed for the latter.
- It is important to calculate incremental cost effectiveness results for both disease-specific and generic outcome measures when conducting economic evaluation of interventions for chronic obstructive pulmonary disease.

### Strengths and Limitations

- Strengths include the study design, the sample size, and the range of resource, cost and economic patient level data collected for analysis.
- Limitations include the time horizon of the analysis which was confined to the trial follow up period, thereby reducing the ability to gauge the longer term effects of treatment.

## ABSTRACT

**Objective:**

To assess the cost effectiveness of a structured education pulmonary rehabilitation programme (SEPRP) for chronic obstructive pulmonary disease (COPD) relative to usual practice in primary care. The programme consisted of one group-based session per week over eight weeks delivered jointly by practice nurses and physiotherapists.

**Design:**

Economic evaluation, employing cost effectiveness and cost utility analysis, alongside a cluster randomised controlled trial.

**Setting:**

32 general practice surgeries in Ireland

**Participants:**

350 adults with COPD, 69% of whom are moderately affected.

**Interventions:**

Intervention arm (n=178) received a two-hour group-based SEPRP session per week over eight weeks delivered jointly by a practice nurse and physiotherapist at the practice surgery or nearby venue. Control arm (n=172) received usual practice in primary care.

**Main Outcome Measures:**

Incremental costs, Chronic Respiratory Questionnaire (CRQ), quality adjusted life years (QALYs) gained estimated using the generic EQ5D instrument, and expected cost effectiveness at 22 weeks trial follow up.

**Results:**

The intervention was associated with an increase of €944 (95% CIs: 489, 1400) in mean healthcare cost and €261 (95% CIs: 226, 296) in mean patient cost. The intervention was associated with a mean improvement of 1.11 (95% CIs: 0.35, 1.87) in CRQ Total score and 0.002 (95% CIs: -0.006, 0.011) in QALYs gained. These translated into incremental cost effectiveness ratios of €850 per unit increase in CRQ Total score and €472,000 per additional QALY gained. The probability of the intervention being cost effective at respective threshold values of €5,000, €15,000, €25,000 €35,000, and €45,000 was 0.980, 0.992, 0.994, 0.994, and


**Comment [i1]:** The Abstract has been altered considerably to include the suggestions of reviewers.

In particular:

More information is provided on the treatment comparators.

We now highlight that the patient cohort were moderately affected by COPD.

We add the ICERs to the results.

Finally, we tone down the results from 'strong favourable' to 'favourable.

0.994 in the CRQ Total score analysis compared to 0.000, 0.001, 0.001, 0.003, and 0.007 in the QALYs gained analysis.

**Conclusions:**

While favourable cost effectiveness results exist when health status was measured using the disease-specific CRQ instrument, no evidence exists when effectiveness was measured in QALYS gained.

**KEY WORDS**:

COPD; Pulmonary Rehabilitation; Structured Education; Cost Effectiveness

**TRIAL REGISTRATION:**

Current Controlled Trials ISRCTN52403063

## INTRODUCTION

Pulmonary rehabilitation is key strategy in the clinical management of chronic obstructive pulmonary disease (COPD) and has been shown to be effective in improving patients' health related quality of life.[1, 2, 3] While much of the established evidence relates to programmes delivered in hospital, outpatient, or home settings,[4,5] there are growing calls for the provision of such services in the primary care setting.[6,7] Nonetheless, further evidence on clinical and cost effectiveness is required before primary care provision can be recommended. The PRINCE study sought to examine the clinical and cost effectiveness of pulmonary rehabilitation for COPD delivered at the level of general practice in Ireland.[8] To this end, the study evaluated a structured education pulmonary rehabilitation programme (SEPRP) intervention based on evidence collected alongside the cluster randomized controlled trial (RCT).[8]. The SEPRP consisted of a two-hour group-based session each week for eight weeks delivered jointly by practice nurses and physiotherapists and was compared in the trial to usual practice in primary care. The primary outcome in the clinical analysis was change in disease-specific health status from baseline to follow up, as measured using the Chronic Respiratory Questionnaire (CRQ) instrument,[9] with results indicating a significant improvement in health status for patients who received the intervention relative to the control of usual care.[10]

In addition to clinical effectiveness, any decision regarding the adoption of a healthcare intervention in clinical practice will depend upon its expected cost effectiveness.[11]The technique of economic evaluation compares the relative cost effectiveness of alternative treatment strategies by relating their mean differences in cost to their mean differences in effectiveness, and by quantifying the uncertainty surrounding these incremental point estimates. Central to this process is the selection of suitable outcome measures which enable the detection of clinically important treatment effects. In addition, and in order to more fully inform priority setting, generic outcome measures are preferable as they enable the comparison of a wide range of programmes across multiple patient populations, all of which may be competing for limited healthcare resources. Notably however, recent evidence has cast doubt on the ability of generic outcome measures to adequately capture meaningful differences in clinical severity for COPD patient populations.[12] Indeed, the adoption of generic rather than disease-specific measures in this context may lead to the underestimation of treatment benefits, biased cost effectiveness results, and ill-informed policy decisions.[13]

**Comment [i2]:** The structure of the Introduction has been altered to reflect the reviewer suggestions.

In particular, the section on the RCT has been moved to the Methods.

The remainder of the Introduction has been altered slightly to reflect this change.

With this in mind, we present and compare cost effectiveness and cost utility results for disease-specific health status, as measured by the CRQ, and generic health status, as measured by quality adjusted life years (QALYs) gained.

## METHODS

### The PRINCE Cluster RCT

Comment [i3]: This section has been moved from the Introduction and has been changed slightly to ensure the flow of the paper.

Full details of the study methods are published elsewhere.[8] In brief, a cluster randomized controlled trial (RCT) recruited 32 general practices and 350 patients with a diagnosis of COPD as defined by the GOLD guidelines.[14] Ethical approval was provided by the local ethics committees at the participating study centres. Practices were randomised to the control group, where patients (n=172) received usual care in general practice, or the intervention group, in which patients (n=178) received a structured education pulmonary rehabilitation programme (SEPRP). The SEPRP consisted of an eight-week programme with a group two-hour session each week delivered jointly by a practice nurse and physiotherapist at the practice surgery or nearby venue. The practice nurse facilitated the educational content of the programme and the physiotherapist focused on delivering the exercise component. The practice nurse also provided on-going advice and support to participants as required throughout the intervention period. In addition, participants were followed-up formally via telephone call at 4 weeks after completion of the SEPRP and via a 1-hour group session at 10 weeks. To facilitate the delivery of the intervention, educators received training via specialised preparation programmes and on-going support from the research team. To ensure standardisation of programme content and delivery, all training was provided by research staff, and educators were audited to ensure adherence to programme principles and content.

Details on the characteristics of the study participants are presented in Appendix Table 1 and were broadly similar across treatment arms.[10] Two patients in the intervention group and 6 patients in the control group died over the course of the trial and are excluded from the analysis, leaving 342 (98%) for the statistical analysis.[10] The primary outcome in the clinical analysis was change in disease-specific health status from baseline to follow up, as measured using the CRQ.[9] At trial follow up, the intervention was associated with statistically significant improvements in CRQ Dyspnoea scores (0.49; 95% CIs: 0.20, 0.78), CRQ Physical scores (0.37; 95% CIs: 0.14, 0.60), and CRQ Total score (1.11; 95% CIs: 0.35,

1.87) relative to the control.[10] There were concerns, however, that the confidence intervals did not exclude differences in effect that were pre-specified as clinically insignificant.[10]

**Economic Evaluation**

The economic evaluation consisted of a trial-based analysis with a time horizon of 22 weeks, the trial follow up period. The perspective of the healthcare provider was adopted with respect to costing and health outcomes were expressed in terms of disease-specific and generic health status. Data are also presented for private patient expenses. Evidence on resource use and health status, specifically CRQ and EQ5D, was collected via structured questionnaires and practice note searches at baseline (for the 26 weeks pre-randomisation) and follow up. Given the length of follow up, neither nether costs nor outcomes were discounted. The statistical analysis was conducted on an intention to treat basis, and in accordance with current guidelines for clinical and cost effectiveness analysis alongside cluster RCTs.[15,16] That is, we adopt statistical techniques which recognise both the clustering and correlation of cost and effect data. The incremental analyses were undertaken using generalised estimating equations (GEE), a flexible multivariate regression framework that explicitly allows for the modelling of normal and non-normal distributional forms of clustered data.[17] Uncertainty in the analysis was addressed by estimating 95% confidence intervals and cost effectiveness acceptability curves, which link the probability of a treatment being cost effective to a range of potential threshold values (λ) that the health system may be willing to pay for an additional unit of effect.[11] In addition, sensitivity analysis was undertaken to examine the effect of conducting a complete case only analysis and of varying the cost of delivering the intervention in practice. All analysis was undertaken using STATA and EXCEL statistical packages.

**Comment [i4]:** The Economic Evaluation Methods have been updated to more clearly present the analysis, as originally undertaken.

Furthermore, we now:

Specify the perspective as that of the health care provider.

State that costs and effects are not discounted – given the limited follow up period.

Include a sensitivity analysis for:
(1)Complete Case Analysis
(2)Reduced Intervention Costs, if the SEPRP was delivered to 15 or 20 patients, up from the average of 11.

**Cost Analysis**

Three cost components were included in the analysis, all of which were expressed in Euros (€) in 2009 prices. The first was the cost of implementing the intervention in clinical practice and included resources relating to: educator and patient recruitment; educator, administrator and patient time input; venue and equipment rental; educational materials and consumables; and post, packaging, telephone and travel expenses (see Appendix Table 2).These costs were allocated to all 178 patients who participated in the SEPRP intervention. In sensitivity analysis, we explore the effect to expanding the number of patients per SEPRP session from

**Comment [i5]:** Further details are presented on the costing process.

an average of 11 to 15, or 240 in total, and 20, or 320 in total, respectively; thereby reducing the intervention cost per patient.

Second, costs relating to the use of primary and secondary healthcare services over the course of the trial were estimated. This included the costs of general practitioner (GP), practice nurse, physiotherapist, dietician, public health nurse, home help, and social worker consultations, outpatient services, accident and emergency (A&E) visits, hospital admissions, COPD medications and oxygen therapy. Third, private costs to patients, in terms of time input and travel expenses over the course of the trial, were included. Resource use was captured via a combination of chart searches and patient questionnaires conducted by research staff at baseline and follow up. A vector of unit costs was applied to calculate the cost associated with each resource activity at baseline and follow up (see Table 1). Unit cost estimates for each activity were based on national data sources and, where necessary, were transformed to Euros (€) in 2009 prices using appropriate indices.[18,19] In particular, unit costs per consultation were obtained from published health service documents while drugs were costed using the monthly index of medical specialties for Ireland.

Two total cost variables were constructed for the incremental analysis: (i) total healthcare cost and (ii) total patient cost. To facilitate this process, imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing values for individual resource use at follow up. While the amount of missing data was very low, we adopted this approach to ensure a more complete analysis. Estimation of incremental costs at follow up was undertaken using GEE regression models controlling for treatment arm, baseline cost, and clustering. To account for the non-normal nature of the cost data, multilevel regression models assuming a gamma variance function were estimated.[20]

**Effectiveness Analysis**

Comment [i6]: Further information is now presented in the CRQ and the Eq5D, as requested.

Health outcomes in the analysis were expressed in terms of disease-specific and generic measures of health status. COPD-specific health status was measured using the CRQ instrument,[9] which consists of 20 items which are subdivided into four domains: dyspnoea, fatigue, emotional function and mastery. The self-administered version of the CRQ with individualized dyspnea domain was used. Individuals were asked to rate each item on a 7-point scale from 1 (maximum impairment) to 7 (no impairment). Each domain is scored as the sum of the individual items.[9] Based on patient responses, three CRQ aggregate scores

can be calculated: (i) CRQ Physical, which is an aggregate of the dyspnoea and fatigue domains; (ii) CRQ Psychological, which is an aggregate of the emotional function and mastery domains; and (iii) CRQ Total, which is an aggregate of all four domains.[9] For the purposes of the economic evaluation, only the CRQ Total score variable was included in the incremental cost effectiveness analysis.

Generic health status was expressed in terms of QALYs gained calculated based on patient responses to the EuroQol EQ5D 3L instrument.[21,22] The EQ5D consists of five dimensions: mobility, self-care, usual activities, pain or discomfort and anxiety or depression; and each dimension has three levels of severity: no problems, moderate problems or extreme problems. EQ5D responses are transformed using an algorithm into a single health state index score, based on values elicited via the time trade-off approach for the UK population,[23,24] which typically range from 0 (equivalent to death) to 1 (equivalent to good health), although a small number of health states are valued as worse than death. EQ5D scores at baseline and follow up were used to calculate patient-specific QALYs gained over 22 weeks using the area under the curve method.[25] Once again, to facilitate this process, imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing values at follow up. Estimation of incremental effectiveness at follow up was undertaken using GEE regression models, assuming a Gaussian variance function, and controlling for treatment arm, baseline EQ5D score, and clustering.

**Comment [i7]:** Further detail is now presented on the regression analysis for the effectiveness analysis.

**Cost Effectiveness Analysis**

To undertake the cost effectiveness analysis, we adopt techniques which recognise both the clustering and correlation of cost and effect data collected alongside cluster RCTs. In economic evaluation, one treatment is defined as more cost effective than its comparator if one of the following conditions apply: (a) it is less costly and more effective; (b) it is more costly and more effective, but its additional cost per additional unit of effect, known as the incremental cost effectiveness ratio (ICER), is considered worth paying by decision makers; or (c) it is less costly and less effective, but the additional cost per additional unit of effect of its comparator is not considered worth paying by decision makers.[11] We employ the net benefit framework,[26] which allows for costs and effectiveness, and their correlation, to be combined into a single variable for each individual, to identify which of these three conditions applies in this case.

We define net benefit (*nb*) as,

$nb_{ijk} = e_{ijk}\lambda - c_{ijk}$,

where $e_{ijk}$ is the health outcome for the $_i$th person in the $_j$th cluster in treatment arm $_k$, λ is the cost effectiveness threshold value, and $c_{ijk}$ is their cost. Using this framework, the intervention is defined to be cost effective, at a given threshold value, λ, if its corresponding net benefit is greater than that of the control: that is, if the incremental net benefit for the intervention minus control is greater than zero.

Net benefit statistics for CRQ Total score and QALYs gained were calculated by relating total healthcare costs to the outcome measures of interest for a series of threshold values (ranging from λ = €0 to €70,000). Imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing CRQ values at follow up. Estimation of incremental net benefit was undertaken using GEE regression models, assuming a Gaussian variance function, and controlling for treatment arm, baseline CRQ or EQ5D score, baseline healthcare cost and clustering. The incremental cost effectiveness results are presented using ICERs and cost effectiveness acceptability curves, which were estimated parametrically,[26] and report the probability that the intervention is more cost effective than the control. The curves incorporate the sampling uncertainty around the ICER estimates as well as the uncertainty around the true threshold value, λ,[27] which is not explicitly known for Ireland.[28]

**Comment [i8]:** Further detail is now presented on the regression analysis for the incremental cost effectiveness analysis.

## RESULTS

**Comment [i9]:**

The Results sections and Tables have been updated.

Table 2 and Table 3 in the main paper and Appendix Table 2 and Appendix Table 3 have been changed to reflect the reviewer comments.

Raw data estimates for resource use, costs and health outcomes at follow up are summarised in Table 2 (for the equivalent baseline results see Appendix Table 3). The cost of the intervention was estimated at €822 per participant, which consisted of €564 in healthcare costs and €258 in patient costs (see Appendix Table 2). Individual resource costs were combined to calculate total costs of care and are presented in Table 3. In terms of total costs over 22 weeks follow up, the mean healthcare cost per patient in the control arm was €1505 (SD: 1872) and €2357 (SD: 3532) in the intervention arm. The equivalent results for total patient cost were €129 (SD: 113) and €380 (SD: 111) respectively.

In terms of disease-specific health status, mean CRQ Total score per patient at follow up was 19.10 (SD: 4.83) in the control arm and 20.82 (SD: 3.88) in the intervention arm (see Table 3). Further results for CRQ domain scores are presented in Table 2 and in Casey et al.[10] In terms of generic health status, mean QALYs gained per patient at 22 weeks was 0.305 (SD: 0.106) in the control arm and 0.337 (SD: 0.081) in the intervention arm (see Table 3).

The results from the incremental analyses are also presented in Table 3. These indicate that the intervention was, on average, associated with higher costs and improved health outcomes, as measured using the CRQ and QALYs, when compared to the control. The intervention was estimated to result in a statistically significant increase in mean cost per patient of €944 (95% CIs: 489, 1400; $p<0.01$) in total healthcare costs and €261 (95% CIs: 226, 296; $p<0.01$) in total patient costs. In respect of effectiveness, the intervention was associated with a statistically significant increase in mean CRQ Total score of 1.11 (95% CIs: 0.35, 1.87; $p<0.01$) per patient and a non-significant increase in mean QALYs gained of 0.002 (95% CIs: -0.006, 0.011; $p=0.63$) per patient.

These results translated into incremental cost effectiveness ratios of €850 per unit increase in CRQ Total score and €472,000 per additional QALY gained. In terms of expected cost effectiveness, the probabilistic results are summarised in Table 3 and presented graphically in Figure 1. These indicate that for the CRQ Total score analysis, the probability of the intervention being more cost effective than the control was 0.980, 0.992, 0.994, 0.994, and 0.994 at threshold values of €5,000, €15,000, €25,000 €35,000, and €45,000 respectively. For the QALYs gained analysis, the equivalent probability estimates were 0.000, 0.001, 0.001, 0.003, and 0.007 respectively. The results from the sensitivity analysis are presented in the appendix and generally conform to the expected cost effectiveness results reported for the primary analysis.

## DISCUSSION

Comment [i10]: The Discussion has been updated to reflect the changes made to the analysis and to incorporate specific suggestions highlighted by the reviwers.

On the basis of evidence collected alongside a cluster RCT, a structured education pulmonary rehabilitation programme for COPD delivered in primary care was, on average, more costly and more effective than usual general practice care. Notably however, while the intervention was associated with statistically significant improvements in disease-specific health status, this was not reflected in generic health status. Moreover, the confidence intervals for the

disease-specific analysis included differences in effect that were deemed clinically insignificant.[10] Given the uncertainty relating to the effectiveness data, there is unsurprisingly conflicting evidence regarding the value for money of the programme. While there is favourable cost effectiveness evidence when outcomes are measured in terms of disease-specific health status, no such evidence exists in relation to generic health status. More specifically, in the cost per CRQ Total score analysis, the probability that the intervention was more cost effective than usual care was 0.980 or greater for a range of potential threshold values, notwithstanding concerns relating to clinical insignificance. In stark contrast, the cost per QALY gained analysis indicates that the intervention is highly unlikely to be deemed cost effective relative to usual care or indeed other programmes inside and outside of COPD medicine.

The ceiling ratios per QALY gained presented provide a useful range for comparison, given the lack of an implicit or explicit values for Ireland, and the current weak evidence base with respect to this type of health economic analysis for Ireland. However, the approach we used in applying the same ceiling rates per unit increase in CRQ gained is problematic as these values may, or may not, be much lower than those presented. In comparison to countries such as the UK, the range of ceiling ratios presented may be too high for CRQ in particular, and it might have been more useful, if somewhat more cumbersome, to present a different range of ceiling ratios for each of the two outcomes. For example, the shape of the CEAC for CRQ would also likely be different if additional points between €0 and €5,000 were evaluated. The difficulty is that in the absence of evidence in regard to an appropriate range of ceiling ratios any decision will appear arbitrary and be open to criticism. As usual, it will ultimately be the responsibility of the relevant policy decision maker to determine whether the evidence presented is sufficient to justify the adoption of the SEPRP intervention in clinical practice. What is clear is that there were significant improvements in CRQ after adjusting for differences in baseline values between intervention and control groups.

This study highlights the complexity of resource allocation decision making in this context as variations in estimated incremental effectiveness have markedly different implications for policy depending on the specificity of the outcome. Indeed, the central question is whether our findings reflect an absence of a clinically significant treatment effect or alternatively a lack of sensitivity in the ability of the generic EQ5D instrument to detect a clinically meaningful improvement in COPD health status. In the case of the former, it is worth noting

that in contrast to the majority of trials included in a Cochrane systematic review,[4] most of the participants in our study had moderate COPD (FEV1 around 55-60% predicted).[10] This is not surprising given that the target COPD population in a primary care setting is, by definition, likely to be less severely affected than hospital-based populations. Overall, our results highlight the need for a better understanding of the relationship between COPD disease-specific and generic outcome measures, the importance of exploring cost effectiveness in terms of both disease-specific and generic health status for this patient population, and the need to consider both measures in the resource allocation decision making process. Indeed, our findings can be added to those of existing studies which explore how the adoption of generic rather than disease-specific measures in this context may lead to the underestimation of treatment benefits, biased cost effectiveness results, and ill-informed policy decisions.[12,13] Moreover, this study highlights the difficulty of identifying an appropriate ceiling ratio and drawing conclusions based on ICERs using non-preference-based measures.

That said, our study adds to the existing literature on the cost effectiveness of pulmonary rehabilitation for COPD by evaluating a programme delivered in primary care. There is a broad literature showing that such programmes are cost effective in various hospital, outpatient and home settings [29-37]. Moreover, it also adds to the growing evidence of cost-effectiveness gains from rehabilitation and self-management programmes delivered in primary care settings for other diseases such as diabetes [38,39] and heart disease.[40] Keeping people out of hospital has been shown to be the key driver in lowering costs in the majority of these studies. Moreover, those studies which have reported cost savings generally adopted time horizons for analysis of one year or more, while we were restricted to a follow up of only 22 weeks. The short-time horizon for our study is, therefore, a significant weakness to exploring the sustainability of the intervention. Extending the time horizon would likely improve the cost-effectiveness of the intervention, linked to lower hospital admissions, if the evidence of other studies can be used as a guide to future resource use in Ireland. It should also be noted that the use of 2009 prices in the analysis may have inflated costs. Medical inflation has fallen in the period since then, which would also likely contribute to an improvement in the cost effectiveness results into the future.

A few other points should be noted as having potential effects on the results of this study. The conduct of economic evaluation in Ireland is complicated by a paucity of relevant data. In

particular, given the lack of utility data the EQ5D instrument was adopted and assumed to be relevant for an Irish population. This may not be the case. The process of conducting cost analysis in Ireland is also compromised by the lack of nationally available unit cost data. In estimating unit costs for individual resource activities, we endeavoured at all times to be conservative in any assumptions adopted. Furthermore, while we employ an appropriate multilevel net benefit regression approach to account for the correlation and clustering in the cost and effect data, arguments could be made for alternative bivariate or non-parametric approaches.[16]

In conclusion, the evidence is contradictory in regard to the cost effectiveness of a structured education programme for COPD delivered in primary care in Ireland. While there appears to be favourable evidence in terms of disease-specific COPD health status, there is no such evidence in relation to generic health status as measured by QALYs. As a result, uncertainty surrounds the policy implications of this analysis. Nonetheless, the study confirms the importance of calculating incremental cost effectiveness results for both disease-specific and generic outcome measures for COPD patient populations.

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**Table 1 – Categories of Resource Use and Unit Cost Estimates in 2009 (€) Prices**

| RESOURCE ITEM | ACTIVITY | UNIT COST €'s | SOURCE |
|---|---|---|---|
| **Healthcare Resources** | | | |
| General Practitioner Visit | Per Consultation | 50 | ORC |
| Practice Nurse Visit | Per Consultation | 12 | DOHC |
| Hospital Admission Visit | Per Inpatient Day | 832 | DOHC |
| Outpatient Clinic Visit | Per Visit | 169 | DOHC |
| Accident and Emergency Clinic Visit | Per Visit | 289 | DOHC |
| Physiotherapist Visit | Per Consultation | 24 | HSE |
| Dietician Visit | Per Consultation | 24 | HSE |
| Public Health Nurse Visit | Per Consultation | 27 | HSE |
| Home Help Visit | Per Consultation | 16 | HSE |
| Social Worker Visit | Per Consultation | 24 | HSE |
| Spiriva (Tiotropium Bromide) | Per Day | 1.42 | MIMS |
| Seretide (Salmeterol, Fluticasone propionate) | Per Day | 2.22 | MIMS |
| Serevent (Salmeterol xinafoate) | Per Day | 0.94 | MIMS |
| Ventolin (Salbutamol Sulfate, Salamol) | Per Day | 0.24 | MIMS |
| Combivent (Ipratropium Bromide-Salbutamol Sulfate) | Per Day | 0.83 | MIMS |
| Singulair (Montelukast) | Per Day | 1.18 | MIMS |
| Becotide (Beclometasone, Beclazone) | Per Day | 0.27 | MIMS |
| Symbicort (Cortisone Inhalers) | Per Day | 1.55 | MIMS |
| Pulmicort (Budesonide) | Per Day | 0.82 | MIMS |
| Bricanyl (Terbutaline Sulfate) | Per Day | 0.21 | MIMS |
| Oral Prednisone (Prednesol, Deltacortril) | Per Day | 0.47 | MIMS |
| Oral Phyollocntin (Aminophylline) | Per Day | 0.28 | MIMS |
| Uniphyl (Theophylline) | Per Day | 0.19 | MIMS |
| Atrovent (Ipratropium bromide) | Per Day | 0.20 | MIMS |
| Oxygen Cylinder | Per Day | 4.91 | Britton et al, 2003 |
| Oxygen Concentrator | Per Day | 2.19 | Britton et al, 2003 |
| | | | |
| **Patient Resources** | | | |
| *Travel Expenses* | | | |
| Car | Per Mile | 1.06 | DOF |
| Bus | Per Mile | 1.64 | Dublin Bus |
| Taxi | Per Fare/Add. Mile | 3.71/1.56 | www.taxi.ie |
| *Time Input* | | | |
| Economically Active | Per Hour | 19 | CSO |
| Economically Inactive | Per Hour | 9 | CSO |

**Note:**
ORC – Office of the Revenue Commissioner, Dublin, Ireland.
DOHC – Casemix Unit, Department of Health and Children, Dublin, Ireland
HSE – Salary Scales, Health Service Executive, Dublin, Ireland
MIMS - Monthly Index of Medical Specialties Ireland, Dublin, Ireland
DOF – Department of Finance, Dublin, Ireland
CSO – Central Statistics Office, Dublin, Ireland

**Comment [i11]:** Further information on the brand and generic names are now provided.

Details on data sources are described in footnotes.

**Table 2 – Raw Data Estimates for Resource Use, Costs and Health Outcomes at 22 Weeks Follow Up**

| VARIABLE | INTEVENTION (N=178) *Mean (SD) / %* | | CONTROL (N=172) *Mean (SD) / %* | |
|---|---|---|---|---|
| **RESOURCE ITEM** | **Usage** | **Cost (€)** | **Usage** | **Cost(€)** |
| **Healthcare Resources** | | | | |
| GP Visits: Breathing Problems | 1.6 (2.0) | 134 (122) | 1.8 (2.5) | 153 (158) |
| GP Visits: Other | 2.4 (2.5) | 118 (124) | 2.7 (2.7) | 133 (136) |
| Practice Nurse Visits: Breathing Problems | 0.1 (0.3) | 1 (4) | 0.1 (0.5) | 2 (6) |
| Practice Nurse Visits: Other | 1.1 (2.0) | 13 (24) | 1.2 (2.1) | 14 (25) |
| Inpatient Days: Breathing Problems | 0.5 (2.8) | 411 (2300) | 0.1 (0.6) | 80 (504) |
| Inpatient Days: Other | 0.4 (2.5) | 336 (2054) | 0.3 (1.9) | 266 (1552) |
| Outpatient Visits: Breathing Problems | 0.2 (0.5) | 36 (90) | 0.3 (0.7) | 52 (124) |
| Outpatient Visits: Other | 0.8 (1.5) | 134 (253) | 0.7 (1.2) | 118 (208) |
| Accident &Emergency Visits: Breathing Problems | 0.1 (0.2) | 12 (57) | 0.1 (0.3) | 17 (76) |
| Accident &Emergency Visits: Other | 0.1 (0.3) | 23 (78) | 0.1 (0.2) | 16 (66) |
| Physiotherapist Visits: Breathing Problems | 0.3 (1.4) | 6 (33) | 0.2 (1.3) | 5 (30) |
| Physiotherapist Visits: Other | 0.5 (1.9) | 11 (46) | 0.5 (1.9) | 11 (45) |
| Public Health Nurse Visits: Breathing Problems | 0.1 (1.0) | 3 (27) | 0.1 (1.0) | 3 (28) |
| Public Health Nurse Visits: Other | 0.3 (1.6) | 8 (42) | 0.4 (1.9) | 12 (51) |
| Dietician Visits | 0.0 (0.2) | 1(4) | 0.0 (0.3) | 1 (6) |
| Home Help Visits | 3.9 (17.5) | 63(280) | 5.4 (20.3) | 87 (325) |
| Social Worker Visits | 0.0 (0.0) | 0 (0) | 0.0 (0.1) | 1 (2) |
| Spiriva | 59% | 138 (115) | 62% | 144 (113) |
| Seretide | 56% | 203 (182) | 55% | 200 (182) |
| Serevent | 1% | 2 (16) | 1% | 1 (12) |
| Ventolin | 53% | 21 (20) | 52% | 20 (20) |
| Combivent | 13% | 18 (46) | 15% | 21 (49) |
| Singulair | 9% | 16 (53) | 11% | 21 (60) |
| Becotide | 4% | 2 (9) | 7% | 3 (11) |
| Symbicort | 18% | 45 (97) | 20% | 50 (102) |
| Pulmicort | 4% | 5 (26) | 5% | 7 (30) |
| Bricanyl | 2% | 1 (5) | 2% | 1 (5) |
| Oral Prednisone | 4% | 3 (15) | 11% | 8 (24) |
| Oral Phyollocntin | 1% | 1 (4) | 3% | 1 (8) |
| Uniphyl | 8% | 3 (8) | 7% | 2 (8) |
| Atrovent | 7% | 2 (8) | 8% | 3 (9) |
| Oxygen Therapy | 3% | 16 (96) | 5% | 26 (121) |
| Intervention | n/a | 564 (n/a) | n/a | 0 (n/a) |
| **Patient Resources** | | | | |
| Travel Expenses | n/a | 88 (89) | n/a | 86 (80) |
| Time Input | n/a | 37 (32) | n/a | 39 (32) |
| Intervention | n/a | 258 (n/a) | n/a | 0 (n/a) |
| **HEALTH OUTCOME** | | | | |
| **Disease Specific Measure** | | | | |
| CRQ Dyspnea Score | 4.42 (1.36) | | 3.85 (1.45) | |
| CRQ Fatigue Score | 4.79 (1.31) | | 4.33 (1.47) | |
| CRQ Emotional Score | 5.62 (1.19) | | 5.24 (1.30) | |
| CRQ Mastery Score | 5.94 (1.11) | | 5.59 (1.30) | |
| CRQ Physical Score | 4.62 (1.10) | | 4.12 (1.29) | |
| CRQ Psychological Score | 5.78 (1.06) | | 5.41 (1.22) | |
| **Generic Measure** | | | | |
| EQ5D Score at Follow up | 0.801 (0.232) | | 0.762 (0.252) | |

**Note:** Eight patients (6 intervention and 2 control) who died over the course of the study were excluded from the analysis. Completeness of cost data: ***Intervention*** - 99% for on primary care utilisation, 99% for secondary care utilisation, 80% for community care utilisation, 99% for medication utilisation, 80% for oxygen therapy utilisation, and 78% for Total Healthcare Cost. ***Control***: 97% 97%, 78%, 97%, 78% and 78% respectively. Completeness of effect data: ***Intervention*** - 80% for CRQ, 80% for EQ5D and 80% for QALY scores. ***Control*** - 78%, 78% and 78% (N=134) respectively.

**Comment [i12]:** Table 2 has been changed. As stated, it should now be clear that the data are raw, unadjusted estimates.

The Total Cost, CRQ and QALY estimates have been removed and moved to Table 3.

The results for baseline are presented in the appendix.

**Table 3 – Incremental Cost Effectiveness Results**

| **COST ANALYSIS** | **INTEVENTION (N=178)** *Mean (SD)* | **CONTROL (N=172)** *Mean (SD)* |
|---|---|---|
| **Healthcare Resources** Total Healthcare Cost per patient (€) | 2357 (3532) | 1505 (1872) |
| **Patient Resources** Total Patient Cost per patient (€) | 380 (111) | 129 (113) |
| | **Incremental Analysis** **Difference in Means (95% CI's) [p-value]** (Intervention versus Control) | |
| **Healthcare Resources** Total Healthcare Cost per patient (€) | 944 (489, 1400) [<0.01] | |
| **Patient Resources** Total Patient Cost per patient (€) | 261 (226, 296) [<0.01] | |
| | | |
| **EFFECTIVENESS ANALYSIS** | **INTEVENTION (N=178)** *Mean (SD)* | **CONTROL (N=172)** *Mean (SD)* |
| **Disease Specific Measures** CRQ Total Score | 20.82 (3.88) | 19.10 (4.83) |
| **Generic Measures** QALYs gained | 0.337 (0.081) | 0.305 (0.106) |
| | **Incremental Analysis** **Difference in Means (95% CI's)[p-value]** (Intervention versus Control) | |
| **Disease Specific Measures** CRQ Total Score | 1.11 (0.35, 1.87) [<0.01] | |
| **Generic Measures** QALYs gained | 0.002 (-0.006, 0.011) [0.63] | |
| | | |
| **COST EFFECTIVENESS ANALYSIS** | **Incremental Cost Effectiveness Ratios** (Difference in Mean Cost / Difference in Mean Effect) | |
| **Disease Specific Measures** Cost per CRQ Total Score (€) | 850 | |
| **Generic Measures** Cost per QALYs gained (€) | 472,000 | |

| **Probability that the Intervention is Cost Effective at Threshold Value (λ)** | | |
|---|---|---|
| **Threshold Value (λ)** | **CRQ Total** | **QALYs gained** |
| **λ = €5,000** | 0.980 | 0.000 |
| **λ = €15,000** | 0.992 | 0.001 |
| **λ = €25,000** | 0.994 | 0.001 |
| **λ = €35,000** | 0.994 | 0.003 |
| **λ = €45,000** | 0.994 | 0.007 |

**Note 1:** Incremental total costs estimated using GEE models assuming Gamma variance function, identify link function, exchangeable correlation, and controlling for treatment arm, baseline value, clustering. Incremental CRQ/QALYs estimated using GEE models assuming Gaussian variance function, identify link function, exchangeable correlation, and controlling for treatment arm, baseline value, and clustering.
**Note 2**: Probabilities for cost effectiveness estimated parametrically using net benefit regression models for analysis at each level of **λ.**

**Comment [i13]:** Table 3 has been changed significantly.

It now includes the Total Cost, Total CRQ. and QALY estimates.

It also include the results from the regression analyses which estimate, after adjusting for baseline values, the incremental costs and effects.

The results from the sensitivity analyses are presented in the appendix.

**Figure 1 - Cost Effectiveness Acceptability Curves**

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**Contributors**

Kathy Murphy, Dympna Casey, Declan Devane, Bernard McCarthy, Adeline Cooney, Lorraine Mee, Collete Kirwan conceived the study and together with John Newell and O'Shea participated in the design of the trial and intervention. Paddy Gillespie and Eamon O'Shea undertook the acquisition, analysis and interpretation of the health economic data and the drafting of the research article. All authors participated in critical revision of the manuscript, and have approved the final version.

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**Ethical approval**

Ethical approval has been granted by the Research Ethics Committee of the National University of Ireland, Galway and the Irish College of General Practitioners (ICGP).

**Competing Interests**

The authors report no competing interests. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: that a research grant from the Health Research Board, Ireland was received to undertake the study, and an unconditional Educational Grant was obtained from Pfizer which provided support services to cover desk-top publication costs for manuals, and support for spirometery. The funders had no part in the design of the study; the collection, analysis, and interpretation of the data; the writing of the report; and the decision to submit the article for publication. All authors declare that no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Data sharing**:

No additional data are available.

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# The cost effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial.



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**COVER SHEET**

**Title**: The cost effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial.

**Short Title:** The PRINCE Study: Cost Effectiveness Analysis

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## ARTICLE SUMMARY

### Article focus

- Pulmonary rehabilitation is a key strategy in the clinical management of chronic obstructive pulmonary disease.
- Little is known about the cost effectiveness of pulmonary rehabilitation for chronic obstructive pulmonary disease delivered in primary care.

### Key messages

- There is disease-specific evidence for the cost effectiveness of a structured education programme for chronic obstructive pulmonary disease delivered in primary care.
- Results depend on whether disease-specific or generic measures of health status are used to judge effectiveness: the programme may be cost effective if society is willing to pay at least €850 per one-point increase for the former; while no such evidence existed for the latter.
- It is important to calculate incremental cost effectiveness results for both disease-specific and generic outcome measures when conducting economic evaluation of interventions for chronic obstructive pulmonary disease.

### Strengths and Limitations

- Strengths include the study design, the sample size, and the range of resource, cost and economic patient level data collected for analysis.
- Limitations include the time horizon of the analysis which was confined to the trial follow up period, thereby reducing the ability to gauge the longer term effects of treatment.

## ABSTRACT

**Objective:**

To assess the cost effectiveness of a structured education pulmonary rehabilitation programme (SEPRP) for chronic obstructive pulmonary disease (COPD) relative to usual practice in primary care. The programme consisted of group-based sessions delivered jointly by practice nurses and physiotherapists over eight weeks.

**Design:**

Cost effectiveness and cost utility analysis alongside a cluster randomised controlled trial

**Setting:**

32 general practices in Ireland

**Participants:**

350 adults with COPD, 69% of whom were moderately affected.

**Interventions:**

Intervention arm (n=178) received a two-hour group-based SEPRP session per week over eight weeks delivered jointly by a practice nurse and physiotherapist at the practice surgery or nearby venue. Control arm (n=172) received usual practice in primary care.

**Main Outcome Measures:**

Incremental costs, Chronic Respiratory Questionnaire (CRQ), quality adjusted life years (QALYs) gained estimated using the generic EQ5D instrument, and expected cost effectiveness at 22 weeks trial follow up.

**Results:**

The intervention was associated with an increase of €944 (95% CIs: 489, 1400) in mean healthcare cost and €261 (95% CIs: 226, 296) in mean patient cost. The intervention was associated with a mean improvement of 1.11 (95% CIs: 0.35, 1.87) in CRQ Total score and 0.002 (95% CIs: -0.006, 0.011) in QALYs gained. These translated into incremental cost effectiveness ratios of €850 per unit increase in CRQ Total score and €472,000 per additional QALY gained. The probability of the intervention being cost effective at respective threshold values of €5,000, €15,000, €25,000 €35,000, and €45,000 was 0.980, 0.992, 0.994, 0.994, and

0.994 in the CRQ Total score analysis compared to 0.000, 0.001, 0.001, 0.003, and 0.007 in the QALYs gained analysis.

**Conclusions:**

While analysis suggests that SEPRP was cost effective if society is willing to pay at least €850 per one-point increase in disease-specific CRQ, no evidence exists when effectiveness was measured in QALYS gained.

**KEY WORDS**:

COPD; Pulmonary Rehabilitation; Structured Education; Cost Effectiveness

**TRIAL REGISTRATION:**

Current Controlled Trials ISRCTN52403063

## INTRODUCTION

Pulmonary rehabilitation is key strategy in the clinical management of chronic obstructive pulmonary disease (COPD) and has been shown to be effective in improving patients' health related quality of life.[1, 2, 3] While much of the established evidence relates to programmes delivered in hospital, outpatient, or home settings,[4,5] there are growing calls for the provision of such services in the primary care setting.[6,7] Nonetheless, further evidence on clinical and cost effectiveness is required before primary care provision can be recommended. The PRINCE study sought to examine the clinical and cost effectiveness of pulmonary rehabilitation for COPD delivered at the level of general practice in Ireland.[8] To this end, the study evaluated a structured education pulmonary rehabilitation programme (SEPRP) intervention based on evidence collected alongside the cluster randomized controlled trial (RCT).[8]. The SEPRP consisted of a two-hour group-based session each week for eight weeks delivered jointly by practice nurses and physiotherapists and was compared in the trial to usual practice in primary care. The primary outcome in the clinical analysis was change in disease-specific health status from baseline to follow up, as measured using the Chronic Respiratory Questionnaire (CRQ) instrument,[9] with results indicating a significant improvement in health status for patients who received the intervention relative to the control of usual care.[10]

In addition to clinical effectiveness, any decision regarding the adoption of a healthcare intervention in clinical practice will depend upon its expected cost effectiveness.[11]The technique of economic evaluation compares the relative cost effectiveness of alternative treatment strategies by relating their mean differences in cost to their mean differences in effectiveness, and by quantifying the uncertainty surrounding these incremental point estimates. Central to this process is the selection of suitable outcome measures which enable the detection of clinically important treatment effects. In addition, and in order to more fully inform priority setting, generic outcome measures are preferable as they enable the comparison of a wide range of programmes across multiple patient populations, all of which may be competing for limited healthcare resources. Notably however, recent evidence has cast doubt on the ability of generic outcome measures to adequately capture meaningful differences in clinical severity for COPD patient populations.[12] Indeed, the adoption of generic rather than disease-specific measures in this context may lead to the underestimation of treatment benefits, biased cost effectiveness results, and ill-informed policy decisions.[13]

With this in mind, we present and compare cost effectiveness and cost utility results for disease-specific health status, as measured by the CRQ, and generic health status, as measured by quality adjusted life years (QALYs) gained.

## METHODS

### The PRINCE Cluster RCT

Full details of the study methods are published elsewhere.[8] In brief, a cluster randomized controlled trial (RCT) recruited 32 general practices and 350 patients with a diagnosis of COPD as defined by the GOLD guidelines.[14] Ethical approval was provided by the local ethics committees at the participating study centres. Practices were randomised to the control group, where patients (n=172) received usual care in general practice, or the intervention group, in which patients (n=178) received a structured education pulmonary rehabilitation programme (SEPRP). The SEPRP consisted of an eight-week programme with a group two-hour session each week delivered jointly by a practice nurse and physiotherapist at the practice surgery or nearby venue. The practice nurse facilitated the educational content of the programme and the physiotherapist focused on delivering the exercise component. The practice nurse also provided on-going advice and support to participants as required throughout the intervention period. In addition, participants were followed-up formally via telephone call at 4 weeks after completion of the SEPRP and via a 1-hour group session at 10 weeks. To facilitate the delivery of the intervention, educators received training via specialised preparation programmes and on-going support from the research team. To ensure standardisation of programme content and delivery, all training was provided by research staff, and educators were audited to ensure adherence to programme principles and content. The control arm in this study was usual care in Irish general practice. However, pulmonary rehabilitation is not currently offered in a systematic manner in primary care in Ireland. A descriptive qualitative analysis revealed that usual care involves patients with COPD attending their GP if they feel unwell and taking their prescribed medications.[10] Indeed, the data we present for the control arm in relation to their healthcare services and medications usage goes to highlight the nature of usual practice in the primary care setting.

Details on the characteristics of the study participants are presented in Appendix Table 1 and were broadly similar across treatment arms.[10] Two patients in the intervention group and 6 patients in the control group died over the course of the trial and are excluded from the

analysis, leaving 342 (98%) for the statistical analysis.[10] The primary outcome in the clinical analysis was change in disease-specific health status from baseline to follow up, as measured using the CRQ.[9] At trial follow up, the intervention was associated with statistically significant improvements in CRQ Dyspnoea scores (0.49; 95% CIs: 0.20, 0.78), CRQ Physical scores (0.37; 95% CIs: 0.14, 0.60), and CRQ Total score (1.11; 95% CIs: 0.35, 1.87) relative to the control.[10] There were concerns, however, that the confidence intervals did not exclude differences in effect that were pre-specified as clinically insignificant.[10]

**Economic Evaluation**

The economic evaluation consisted of a trial-based analysis with a time horizon of 22 weeks, the trial follow up period. The perspective of the healthcare provider was adopted with respect to costing and health outcomes were expressed in terms of disease-specific and generic health status. Data are also presented for private patient expenses. Evidence on resource use and health status, specifically CRQ and EQ5D, was collected via structured questionnaires and practice note searches at baseline (for the 26 weeks pre-randomisation) and follow up (at 22 weeks post randomisation). Given the length of follow up, neither nether costs nor outcomes were discounted. The statistical analysis was conducted on an intention to treat basis, and in accordance with current guidelines for clinical and cost effectiveness analysis alongside cluster RCTs.[15,16] That is, we adopt statistical techniques which recognise both the clustering and correlation of cost and effect data. The incremental analyses were undertaken using generalised estimating equations (GEE), a flexible multivariate regression framework that explicitly allows for the modelling of normal and non-normal distributional forms of clustered data.[17] Uncertainty in the analysis was addressed by estimating 95% confidence intervals and cost effectiveness acceptability curves, which link the probability of a treatment being cost effective to a range of potential threshold values ($\lambda$) that the health system may be willing to pay for an additional unit of effect.[11] In addition, sensitivity analysis was undertaken to examine the effect of conducting a complete case only analysis and of varying the cost of delivering the intervention in practice. All analysis was undertaken using STATA and EXCEL statistical packages.

**Cost Analysis**

Three cost components were included in the analysis, all of which were expressed in Euros (€) in 2009 prices. The first was the cost of implementing the intervention in clinical practice and included resources relating to: educator and patient recruitment; educator, administrator

and patient time input; venue and equipment rental; educational materials and consumables; and post, packaging, telephone and travel expenses (see Appendix Table 2).These costs were allocated to all 178 patients who participated in the SEPRP intervention. In sensitivity analysis, we explore the effect to expanding the number of patients per SEPRP session from an average of 11 to 15, or 240 in total, and 20, or 320 in total, respectively; thereby reducing the intervention cost per patient.

Second, costs relating to the use of primary and secondary healthcare services over the course of the trial were estimated. This included the costs of general practitioner (GP), practice nurse, physiotherapist, dietician, public health nurse, home help, and social worker consultations, outpatient services, accident and emergency (A&E) visits, hospital admissions, COPD medications and oxygen therapy. Third, private costs to patients, in terms of time input and travel expenses over the course of the trial, were included.

Resource use was captured via a combination of electronic chart searches and patient questionnaires conducted by research staff at baseline and follow up. A vector of unit costs was applied to calculate the cost associated with each resource activity at baseline and follow up (see Table 1). Unit cost estimates for each activity were based on national data sources and, where necessary, were transformed to Euros (€) in 2009 prices using appropriate indices.[18,19] In particular, unit costs per consultation were obtained from published health service documents while drugs were costed using the monthly index of medical specialties for Ireland. Two total cost variables were constructed for the incremental analysis: (i) total healthcare cost and (ii) total patient cost. To facilitate this process, imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing values for individual resource use at follow up. Imputation for resource use was undertaken using the *uvis* command in STATA 11, based on a single imputed dataset, and assuming a non-normal distribution for each dependent variable. While the amount of missing data was very low, we adopted this approach to ensure a more complete analysis. Estimation of incremental costs at follow up was undertaken using GEE regression models controlling for treatment arm, baseline cost, and clustering. To account for the non-normal nature of the cost data, multilevel regression models assuming a gamma variance function were estimated.[20]

**Effectiveness Analysis**

Health outcomes in the analysis were expressed in terms of disease-specific and generic measures of health status. COPD-specific health status was measured using the CRQ instrument,[9] which consists of 20 items which are subdivided into four domains: dyspnoea, fatigue, emotional function and mastery. The self-administered version of the CRQ with individualized dyspnea domain was used. Individuals were asked to rate each item on a 7-point scale from 1 (maximum impairment) to 7 (no impairment). Each domain is scored as the sum of the individual items.[9] Based on patient responses, three CRQ aggregate scores can be calculated: (i) CRQ Physical, which is an aggregate of the dyspnoea and fatigue domains; (ii) CRQ Psychological, which is an aggregate of the emotional function and mastery domains; and (iii) CRQ Total, which is an aggregate of all four domains.[9] For the purposes of the economic evaluation, only the CRQ Total score variable was included in the incremental cost effectiveness analysis.

Generic health status was expressed in terms of QALYs gained calculated based on patient responses to the EuroQol EQ5D 3L instrument.[21,22] The EQ5D consists of five dimensions: mobility, self-care, usual activities, pain or discomfort and anxiety or depression; and each dimension has three levels of severity: no problems, moderate problems or extreme problems. EQ5D responses are transformed using an algorithm into a single health state index score, based on values elicited via the time trade-off approach for the UK population,[23,24] which typically range from 0 (equivalent to death) to 1 (equivalent to good health), although a small number of health states are valued as worse than death. EQ5D scores at baseline and follow up were used to calculate patient-specific QALYs gained over 22 weeks using the area under the curve method.[25] Once again, to facilitate this process, imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing values at follow up. Imputation was undertaken using the *uvis* command in STATA 11 and based on a single imputed dataset. Estimation of incremental effectiveness at follow up was undertaken using GEE regression models, assuming a Gaussian variance function, and controlling for treatment arm, baseline EQ5D score, and clustering.

**Cost Effectiveness Analysis**

To undertake the cost effectiveness analysis, we adopt techniques which recognise both the clustering and correlation of cost and effect data collected alongside cluster RCTs. In economic evaluation, one treatment is defined as more cost effective than its comparator if

one of the following conditions apply: (a) it is less costly and more effective; (b) it is more costly and more effective, but its additional cost per additional unit of effect, known as the incremental cost effectiveness ratio (ICER), is considered worth paying by decision makers; or (c) it is less costly and less effective, but the additional cost per additional unit of effect of its comparator is not considered worth paying by decision makers.[11] We employ the net benefit framework,[26] which allows for costs and effectiveness, and their correlation, to be combined into a single variable for each individual, to identify which of these three conditions applies in this case.

We define net benefit (*nb*) as,

$$nb_{ijk} = e_{ijk}\lambda - c_{ijk},$$

where $e_{ijk}$ is the health outcome for the $_i$th person in the $_j$th cluster in treatment arm $_k$, $\lambda$ is the cost effectiveness threshold value, and $c_{ijk}$ is their cost. Using this framework, the intervention is defined to be cost effective, at a given threshold value, $\lambda$, if its corresponding net benefit is greater than that of the control: that is, if the incremental net benefit for the intervention minus control is greater than zero.

Net benefit statistics for CRQ Total score and QALYs gained were calculated by relating total healthcare costs to the outcome measures of interest for a series of threshold values (ranging from $\lambda$ = €0 to €70,000). Imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing CRQ values at follow up. Estimation of incremental net benefit was undertaken using GEE regression models, assuming a Gaussian variance function, and controlling for treatment arm, baseline CRQ or EQ5D score, baseline healthcare cost and clustering. The incremental cost effectiveness results are presented using ICERs and cost effectiveness acceptability curves, which were estimated parametrically,[26] and report the probability that the intervention is more cost effective than the control. The curves incorporate the sampling uncertainty around the ICER estimates as well as the uncertainty around the true threshold value, $\lambda$,[27] which is not explicitly known for Ireland.[28]

**RESULTS**

Raw data estimates for resource use, costs and health outcomes at follow up are summarised in Table 2 (for the equivalent baseline results see Appendix Table 3). Information on missing data is presented in the table footnotes. The cost of the intervention was estimated at €822 per participant, which consisted of €564 in healthcare costs and €258 in patient costs (see Appendix Table 2). Individual resource costs were combined to calculate total costs of care and are presented in Table 3. In terms of total costs over 22 weeks follow up, the mean unadjusted healthcare cost per patient in the control arm was €1505 (SD: 1872) and €2357 (SD: 3532) in the intervention arm. The equivalent results for unadjusted total patient cost over 22 weeks follow up were €129 (SD: 113) and €380 (SD: 111) respectively.

In terms of disease-specific health status, mean unadjusted CRQ Total score per patient at 22 weeks follow up was 19.10 (SD: 4.83) in the control arm and 20.82 (SD: 3.88) in the intervention arm (see Table 3). Further results for CRQ domain scores are presented in Table 2 and in Casey et al.[10] In terms of generic health status, mean unadjusted QALYs gained per patient at 22 weeks was 0.305 (SD: 0.106) in the control arm and 0.337 (SD: 0.081) in the intervention arm (see Table 3).

The results from the incremental analyses are also presented in Table 3. These indicate that the intervention was, on average, associated with higher costs and improved health outcomes, as measured using the CRQ and QALYs, when compared to the control. The intervention was estimated to result in a statistically significant increase in mean cost per patient of €944 (95% CIs: 489, 1400) in total healthcare costs and €261 (95% CIs: 226, 296) in total patient costs. Both estimates were adjusted to account for differences in baseline costs across groups. In respect of effectiveness, the intervention was associated with a statistically significant increase in mean CRQ Total score of 1.11 (95% CIs: 0.35, 1.87) per patient and a non-significant increase in mean QALYs gained of 0.002 (95% CIs: -0.006, 0.011) per patient. Similarly, both estimates were adjusted to account for baseline differences across groups

These results translated into incremental cost effectiveness ratios of €850 per unit increase in CRQ Total score and €472,000 per additional QALY gained. In terms of expected cost effectiveness, the probabilistic results are summarised in Table 3 and presented graphically in Figure 1. These indicate that for the CRQ Total score analysis, the probability of the intervention being more cost effective than the control was 0.980, 0.992, 0.994, 0.994, and 0.994 at threshold values of €5,000, €15,000, €25,000 €35,000, and €45,000 respectively. For

the QALYs gained analysis, the equivalent probability estimates were 0.000, 0.001, 0.001, 0.003, and 0.007 respectively. The results from the sensitivity analysis are presented in the appendix and generally conform to the expected cost effectiveness results reported for the primary analysis.

## DISCUSSION

On the basis of evidence collected alongside a cluster RCT, a structured education pulmonary rehabilitation programme for COPD delivered in primary care was, on average, more costly and more effective than usual general practice care. Notably however, while the intervention was associated with statistically significant improvements in disease-specific health status, this was not reflected in generic health status. Moreover, the confidence intervals for the disease-specific analysis included differences in effect that were deemed clinically insignificant.[10] Given the uncertainty relating to the effectiveness data, there is unsurprisingly conflicting evidence regarding the value for money of the programme. While the cost effectiveness evidence suggests that the programme may be cost effective when outcomes are measured in terms of disease-specific health status and if society is willing to pay at least €850 per one-point increase in CRQ, no such evidence exists in relation to generic health status. More specifically, in the cost per CRQ Total score analysis, the probability that the intervention was more cost effective than usual care was 0.980 or greater for a range of potential threshold values, notwithstanding concerns relating to clinical insignificance. In stark contrast, the cost per QALY gained analysis indicates that the intervention is highly unlikely to be deemed cost effective relative to usual care or indeed other programmes inside and outside of COPD medicine.

The ceiling ratios per QALY gained presented provide a useful range for comparison, given the lack of an implicit or explicit values for Ireland, and the current weak evidence base with respect to this type of health economic analysis for Ireland. However, the approach we used in applying the same ceiling rates per unit increase in CRQ gained is problematic as these values may, or may not, be much lower than those presented. In comparison to countries such as the UK, the range of ceiling ratios presented may be too high for CRQ in particular, and it might have been more useful, if somewhat more cumbersome, to present a different range of ceiling ratios for each of the two outcomes. For example, the shape of the CEAC for CRQ is likely to be different if additional points between €0 and €5,000 were evaluated.

Indeed the probability of the intervention being more cost effective than the control was 0.087, 0.571, 0.900, and 0.995 at threshold values of €500, €1,000, €2,000 and €4,000 respectively. The difficulty is that in the absence of evidence in regard to an appropriate range of ceiling ratios any decision will appear arbitrary and be open to criticism. As usual, it will ultimately be the responsibility of the relevant policy decision maker to determine whether the evidence presented is sufficient to justify the adoption of the SEPRP intervention in clinical practice. What is clear is that there were significant improvements in CRQ after adjusting for differences in baseline values between intervention and control groups.

This study highlights the complexity of resource allocation decision making in this context as variations in estimated incremental effectiveness have markedly different implications for policy depending on the specificity of the outcome. Indeed, the central question is whether our findings reflect an absence of a clinically significant treatment effect or alternatively a lack of sensitivity in the ability of the generic EQ5D instrument to detect a clinically meaningful improvement in COPD health status. In the case of the former, it is worth noting that in contrast to the majority of trials included in a Cochrane systematic review,[4] most of the participants in our study had moderate COPD (FEV1 around 55-60% predicted).[10] This is not surprising given that the target COPD population in a primary care setting is, by definition, likely to be less severely affected than hospital-based populations. Overall, our results highlight the need for a better understanding of the relationship between COPD disease-specific and generic outcome measures, the importance of exploring cost effectiveness in terms of both disease-specific and generic health status for this patient population, and the need to consider both measures in the resource allocation decision making process. Indeed, our findings can be added to those of existing studies which explore how the adoption of generic rather than disease-specific measures in this context may lead to the underestimation of treatment benefits, biased cost effectiveness results, and ill-informed policy decisions.[12,13] Moreover, this study highlights the difficulty of identifying an appropriate ceiling ratio and drawing conclusions based on ICERs using non-preference-based measures.

That said, our study adds to the existing literature on the cost effectiveness of pulmonary rehabilitation for COPD by evaluating a programme delivered in primary care. There is a broad literature showing that such programmes are cost effective in various hospital, outpatient and home settings [29-37]. Moreover, it also adds to the growing evidence of cost-

effectiveness gains from rehabilitation and self-management programmes delivered in primary care settings for other diseases such as diabetes [38,39] and heart disease.[40] Keeping people out of hospital has been shown to be the key driver in lowering costs in the majority of these studies. Moreover, those studies which have reported cost savings generally adopted time horizons for analysis of one year or more, while we were restricted to a follow up of only 22 weeks. The short-time horizon for our study is, therefore, a significant weakness to exploring the sustainability of the intervention. Extending the time horizon would likely improve the cost-effectiveness of the intervention, linked to lower hospital admissions, if the evidence of other studies can be used as a guide to future resource use in Ireland. It should also be noted that the use of 2009 prices in the analysis may have inflated costs. Medical inflation has fallen in the period since then, which would also likely contribute to an improvement in the cost effectiveness results into the future.

A few other points should be noted as having potential effects on the results of this study. Participants were randomised to control and intervention following the collection of baseline data and the demographic data indicated that both groups were well matched.[10] However, there was no feasible way to blind the intervention group to participants or to those facilitating the programme and the study is open to a risk of performance bias. Nevertheless, outcome assessment was blinded thus minimising risks to detection bias. In addition, patients with very severe COPD were excluded due to concerns for their safety and health risks.[8] This is not unusual for trials, in which obtaining a homogenous sample is prioritised, although it does raise concerns as to the generalizability of the findings presented. From an equity perspective, the programme was delivered free at the point of use to all participants ensuring that no one was excluded on the basis of inability to pay. Importantly, patients who died over the course of the trial were excluded from the statistical analysis. This was a pragmatic decision by study researchers on the basis of the trial follow up being limited to 22 weeks and the need to explicitly avoid ascribing differences across groups to the alternative treatments. While this may introduce bias, we do not believe that it would fundamentally alter the results as presented.

The conduct of economic evaluation in Ireland is complicated by a paucity of relevant data. In particular, given the lack of utility data the EQ5D instrument was adopted and assumed to be relevant for an Irish population. This may not be the case. The process of conducting cost analysis in Ireland is also compromised by the lack of nationally available unit cost data. In

estimating unit costs for individual resource activities, we endeavoured at all times to be conservative in any assumptions adopted. Furthermore, while we employ an appropriate multilevel net benefit regression approach to account for the correlation and clustering in the cost and effect data, arguments could be made for alternative bivariate or non-parametric approaches.[16] Moreover, while imputation was deemed necessary for the analysis the approach adopted may be criticised as we imputed values for costs and effects independently. Finally, our analysis is limited by the fact that it is based mainly on data collected using a single trial. While this was deemed sufficient to consider the research question from an Irish perspective, our results would need to be analysed in combination with other international studies to explore the cost effectiveness of pulmonary rehabilitation for COPD in primary care.

In conclusion, the evidence is contradictory in regard to the cost effectiveness of a structured education programme for COPD delivered in primary care in Ireland. While there appears to be evidence in support of the programme if society is willing to pay at least €850 per one-point increase in disease-specific COPD health status, there is no such evidence in relation to generic health status as measured by QALYs. As a result, uncertainty surrounds the policy implications of this analysis. Nonetheless, the study confirms the importance of calculating incremental cost effectiveness results for both disease-specific and generic outcome measures for COPD patient populations.

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**Table 1 – Categories of Resource Use and Unit Cost Estimates in 2009 (€) Prices**

| RESOURCE ITEM | ACTIVITY | UNIT COST €'s | SOURCE |
|---|---|---|---|
| **Healthcare Resources** | | | |
| General Practitioner Visit | Per Consultation | 50 | ORC |
| Practice Nurse Visit | Per Consultation | 12 | DOHC |
| Hospital Admission Visit | Per Inpatient Day | 832 | DOHC |
| Outpatient Clinic Visit | Per Visit | 169 | DOHC |
| Accident and Emergency Clinic Visit | Per Visit | 289 | DOHC |
| Physiotherapist Visit | Per Consultation | 24 | HSE |
| Dietician Visit | Per Consultation | 24 | HSE |
| Public Health Nurse Visit | Per Consultation | 27 | HSE |
| Home Help Visit | Per Consultation | 16 | HSE |
| Social Worker Visit | Per Consultation | 24 | HSE |
| Spiriva (Tiotropium Bromide) | Per Day | 1.42 | MIMS |
| Seretide (Salmeterol, Fluticasone propionate) | Per Day | 2.22 | MIMS |
| Serevent (Salmeterol xinafoate) | Per Day | 0.94 | MIMS |
| Ventolin (Salbutamol Sulfate, Salamol) | Per Day | 0.24 | MIMS |
| Combivent (Ipratropium Bromide-Salbutamol Sulfate) | Per Day | 0.83 | MIMS |
| Singulair (Montelukast) | Per Day | 1.18 | MIMS |
| Becotide (Beclometasone, Beclazone) | Per Day | 0.27 | MIMS |
| Symbicort (Cortisone Inhalers) | Per Day | 1.55 | MIMS |
| Pulmicort (Budesonide) | Per Day | 0.82 | MIMS |
| Bricanyl (Terbutaline Sulfate) | Per Day | 0.21 | MIMS |
| Oral Prednisone (Prednesol, Deltacortril) | Per Day | 0.47 | MIMS |
| Oral Phyollocntin (Aminophylline) | Per Day | 0.28 | MIMS |
| Uniphyl (Theophylline) | Per Day | 0.19 | MIMS |
| Atrovent (Ipratropium bromide) | Per Day | 0.20 | MIMS |
| Oxygen Cylinder | Per Day | 4.91 | Britton et al, 2003 |
| Oxygen Concentrator | Per Day | 2.19 | Britton et al, 2003 |
| | | | |
| **Patient Resources** | | | |
| *Travel Expenses* | | | |
| Car | Per Mile | 1.06 | DOF |
| Bus | Per Mile | 1.64 | Dublin Bus |
| Taxi | Per Fare/Add. Mile | 3.71/1.56 | www.taxi.ie |
| *Time Input* | | | |
| Economically Active | Per Hour | 19 | CSO |
| Economically Inactive | Per Hour | 9 | CSO |

**Note:**
ORC – Office of the Revenue Commissioner, Dublin, Ireland.
DOHC – Casemix Unit, Department of Health and Children, Dublin, Ireland
HSE – Salary Scales, Health Service Executive, Dublin, Ireland
MIMS - Monthly Index of Medical Specialties Ireland, Dublin, Ireland
DOF – Department of Finance, Dublin, Ireland
CSO – Central Statistics Office, Dublin, Ireland

**Table 2 – Raw Data Estimates at Follow Up for Resource Use and Costs (both estimated for the 22 weeks following randomisation) and Health Outcomes.**

| VARIABLE | INTEVENTION (N=178) *Mean (SD) / %* | | CONTROL (N=172) *Mean (SD) / %* | |
|---|---|---|---|---|
| **RESOURCE ITEM** | **Usage** | **Cost (€)** | **Usage** | **Cost(€)** |
| **Healthcare Resources** | | | | |
| GP Visits: Breathing Problems | 1.6 (2.0) | 134 (122) | 1.8 (2.5) | 153 (158) |
| GP Visits: Other | 2.4 (2.5) | 118 (124) | 2.7 (2.7) | 133 (136) |
| Practice Nurse Visits: Breathing Problems | 0.1 (0.3) | 1 (4) | 0.1 (0.5) | 2 (6) |
| Practice Nurse Visits: Other | 1.1 (2.0) | 13 (24) | 1.2 (2.1) | 14 (25) |
| Inpatient Days: Breathing Problems | 0.5 (2.8) | 411 (2300) | 0.1 (0.6) | 80 (504) |
| Inpatient Days: Other | 0.4 (2.5) | 336 (2054) | 0.3 (1.9) | 266 (1552) |
| Outpatient Visits: Breathing Problems | 0.2 (0.5) | 36 (90) | 0.3 (0.7) | 52 (124) |
| Outpatient Visits: Other | 0.8 (1.5) | 134 (253) | 0.7 (1.2) | 118 (208) |
| Accident &Emergency Visits: Breathing Problems | 0.1 (0.2) | 12 (57) | 0.1 (0.3) | 17 (76) |
| Accident &Emergency Visits: Other | 0.1 (0.3) | 23 (78) | 0.1 (0.2) | 16 (66) |
| Physiotherapist Visits: Breathing Problems | 0.3 (1.4) | 6 (33) | 0.2 (1.3) | 5 (30) |
| Physiotherapist Visits: Other | 0.5 (1.9) | 11 (46) | 0.5 (1.9) | 11 (45) |
| Public Health Nurse Visits: Breathing Problems | 0.1 (1.0) | 3 (27) | 0.1 (1.0) | 3 (28) |
| Public Health Nurse Visits: Other | 0.3 (1.6) | 8 (42) | 0.4 (1.9) | 12 (51) |
| Dietician Visits | 0.0 (0.2) | 1(4) | 0.0 (0.3) | 1 (6) |
| Home Help Visits | 3.9 (17.5) | 63(280) | 5.4 (20.3) | 87 (325) |
| Social Worker Visits | 0.0 (0.0) | 0 (0) | 0.0 (0.1) | 1 (2) |
| Spiriva | 59% | 138 (115) | 62% | 144 (113) |
| Seretide | 56% | 203 (182) | 55% | 200 (182) |
| Serevent | 1% | 2 (16) | 1% | 1 (12) |
| Ventolin | 53% | 21 (20) | 52% | 20 (20) |
| Combivent | 13% | 18 (46) | 15% | 21 (49) |
| Singulair | 9% | 16 (53) | 11% | 21 (60) |
| Becotide | 4% | 2 (9) | 7% | 3 (11) |
| Symbicort | 18% | 45 (97) | 20% | 50 (102) |
| Pulmicort | 4% | 5 (26) | 5% | 7 (30) |
| Bricanyl | 2% | 1 (5) | 2% | 1 (5) |
| Oral Prednisone | 4% | 3 (15) | 11% | 8 (24) |
| Oral Phyollocntin | 1% | 1 (4) | 3% | 1 (8) |
| Uniphyl | 8% | 3 (8) | 7% | 2 (8) |
| Atrovent | 7% | 2 (8) | 8% | 3 (9) |
| Oxygen Therapy | 3% | 16 (96) | 5% | 26 (121) |
| Intervention | n/a | 564 (n/a) | n/a | 0 (n/a) |
| **Patient Resources** | | | | |
| Travel Expenses | n/a | 88 (89) | n/a | 86 (80) |
| Time Input | n/a | 37 (32) | n/a | 39 (32) |
| Intervention | n/a | 258 (n/a) | n/a | 0 (n/a) |
| **HEALTH OUTCOME** | | | | |
| **Disease Specific Measure** | | | | |
| CRQ Dyspnea Score | 4.42 (1.36) | | 3.85 (1.45) | |
| CRQ Fatigue Score | 4.79 (1.31) | | 4.33 (1.47) | |
| CRQ Emotional Score | 5.62 (1.19) | | 5.24 (1.30) | |
| CRQ Mastery Score | 5.94 (1.11) | | 5.59 (1.30) | |
| CRQ Physical Score | 4.62 (1.10) | | 4.12 (1.29) | |
| CRQ Psychological Score | 5.78 (1.06) | | 5.41 (1.22) | |
| **Generic Measure** | | | | |
| EQ5D Score | 0.801 (0.232) | | 0.762 (0.252) | |

**Note 1:** Raw data have not been adjusted for baseline values and do not include imputations for missing values.
**Note 2:** Eight patients (6 intervention and 2 control) who died over the course of the study were excluded from the analysis. Completeness of cost data: ***Intervention*** - 99% for on primary care utilisation, 99% for secondary care utilisation, 80% for community care utilisation, 99% for medication utilisation, 80% for oxygen therapy utilisation, and 78% for Total Healthcare Cost. ***Control***: 97% 97%, 78%, 97%, 78% and 78% respectively. Completeness of effect data: ***Intervention*** - 80% for CRQ, 80% for EQ5D and 80% for QALY scores. ***Control*** - 78%, 78% and 78% (N=134) respectively.

**Table 3 – Incremental Cost Effectiveness Results**

| **COST ANALYSIS** | **INTEVENTION (N=178)** *Mean (SD)* | **CONTROL (N=172)** *Mean (SD)* |
|---|---|---|
| **Healthcare Resources** Total Healthcare Cost per patient (€) | 2357 (3532) | 1505 (1872 |
| **Patient Resources** Total Patient Cost per patient (€) | 380 (111) | 129 (113) |
| | **Incremental Analysis** **Difference in Means (95% CI's) [p-value]** (Intervention versus Control) | |
| **Healthcare Resources** Total Healthcare Cost per patient (€) | 944 (489, 1400) [<0.01] | |
| **Patient Resources** Total Patient Cost per patient (€) | 261 (226, 296) [<0.01] | |
| | | |
| **EFFECTIVENESS ANALYSIS** | **INTEVENTION (N=178)** *Mean (SD)* | **CONTROL (N=172)** *Mean (SD)* |
| **Disease Specific Measures** CRQ Total Score | 20.82 (3.88) | 19.10 (4.83) |
| **Generic Measures** QALYs gained | 0.337 (0.081) | 0.305 (0.106) |
| | **Incremental Analysis** **Difference in Means (95% CI's)[p-value]** (Intervention versus Control) | |
| **Disease Specific Measures** CRQ Total Score | 1.11 (0.35, 1.87) [<0.01] | |
| **Generic Measures** QALYs gained | 0.002 (-0.006, 0.011) [0.63] | |
| | | |
| **COST EFFECTIVENESS ANALYSIS** | **Incremental Cost Effectiveness Ratios** (Difference in Mean Cost / Difference in Mean Effect) | |
| **Disease Specific Measures** Cost per CRQ Total Score (€) | 850 | |
| **Generic Measures** Cost per QALYs gained (€) | 472,000 | |
| **Probability that the Intervention is Cost Effective at Threshold Value (λ)** | | |
| **Threshold Value (λ)** | **CRQ Total** | **QALYs gained** |
| **λ = €5,000** | 0.980 | 0.000 |
| **λ = €15,000** | 0.992 | 0.001 |
| **λ = €25,000** | 0.994 | 0.001 |
| **λ = €35,000** | 0.994 | 0.003 |
| **λ = €45,000** | 0.994 | 0.007 |

**Note 1**: Reported estimates for total costs, CRQ and QALYs include imputed values for missing data.
**Note 2**: Reported estimates for incremental differences in costs and effects adjusted to account for baseline difference between groups.
**Note 3:** Regression models for total costs analyses estimated using GEE models assuming Gamma variance function, identify link function, exchangeable correlation, and controlling for treatment arm, baseline value, clustering.
**Note 4:** Regression models for CRQ, QALYs and Net Benefit estimated using GEE models assuming Gaussian variance function, identify link function, exchangeable correlation, and controlling for treatment arm, baseline value, and clustering.
**Note 5**: Incremental cost effectiveness analyses adopt healthcare provider perspective and exclude private patient costs.
**Note 6**: Probabilities for cost effectiveness **e**stimated parametrically using net benefit regression models for analysis at each level of **λ.**

**Figure 1 - Cost Effectiveness Acceptability Curves**

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**Contributors**

Kathy Murphy, Dympna Casey, Declan Devane, Bernard McCarthy, Adeline Cooney, Lorraine Mee, Collete Kirwan conceived the study and together with John Newell and O'Shea participated in the design of the trial and intervention. Paddy Gillespie and Eamon O'Shea undertook the acquisition, analysis and interpretation of the health economic data and the drafting of the research article. All authors participated in critical revision of the manuscript, and have approved the final version.

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**Ethical approval**

Ethical approval has been granted by the Research Ethics Committee of the National University of Ireland, Galway and the Irish College of General Practitioners (ICGP).

**Competing Interests**

The authors report no competing interests. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: that a research grant from the Health Research Board, Ireland was received to undertake the study, and an unconditional Educational Grant was obtained from Pfizer which provided support services to cover desk-top publication costs for manuals, and support for spirometery. The funders had no part in the design of the study; the collection, analysis, and interpretation of the data; the writing of the report; and the decision to submit the article for publication. All authors declare that no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Data sharing**:

No additional data are available.

**COVER SHEET**

**Title**: The cost effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial.

**Short Title:** The PRINCE Study: Cost Effectiveness Analysis

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## ARTICLE SUMMARY

### Article focus

- Pulmonary rehabilitation is a key strategy in the clinical management of chronic obstructive pulmonary disease.
- Little is known about the cost effectiveness of pulmonary rehabilitation for chronic obstructive pulmonary disease delivered in primary care.

### Key messages

- There is disease-specific evidence for the cost effectiveness of a structured education programme for chronic obstructive pulmonary disease delivered in primary care.
- Results depend on whether disease-specific or generic measures of health status are used to judge effectiveness: the programme may be cost effective if society is willing to pay at least €850 per one-point increase for the former; while no such evidence existed for the latter.
- It is important to calculate incremental cost effectiveness results for both disease-specific and generic outcome measures when conducting economic evaluation of interventions for chronic obstructive pulmonary disease.

Comment [i1]: The findings from the study have now been significantly toned down to reflect the comments by the reviewer.

### Strengths and Limitations

- Strengths include the study design, the sample size, and the range of resource, cost and economic patient level data collected for analysis.
- Limitations include the time horizon of the analysis which was confined to the trial follow up period, thereby reducing the ability to gauge the longer term effects of treatment.

## ABSTRACT

**Objective:**

To assess the cost effectiveness of a structured education pulmonary rehabilitation programme (SEPRP) for chronic obstructive pulmonary disease (COPD) relative to usual practice in primary care. The programme consisted of group-based sessions delivered jointly by practice nurses and physiotherapists over eight weeks.

**Design:**

Cost effectiveness and cost utility analysis alongside a cluster randomised controlled trial

**Setting:**

32 general practices in Ireland

**Participants:**

350 adults with COPD, 69% of whom were moderately affected.

**Interventions:**

Intervention arm (n=178) received a two-hour group-based SEPRP session per week over eight weeks delivered jointly by a practice nurse and physiotherapist at the practice surgery or nearby venue. Control arm (n=172) received usual practice in primary care.

**Main Outcome Measures:**

Incremental costs, Chronic Respiratory Questionnaire (CRQ), quality adjusted life years (QALYs) gained estimated using the generic EQ5D instrument, and expected cost effectiveness at 22 weeks trial follow up.

**Results:**

The intervention was associated with an increase of €944 (95% CIs: 489, 1400) in mean healthcare cost and €261 (95% CIs: 226, 296) in mean patient cost. The intervention was associated with a mean improvement of 1.11 (95% CIs: 0.35, 1.87) in CRQ Total score and 0.002 (95% CIs: -0.006, 0.011) in QALYs gained. These translated into incremental cost effectiveness ratios of €850 per unit increase in CRQ Total score and €472,000 per additional QALY gained. The probability of the intervention being cost effective at respective threshold values of €5,000, €15,000, €25,000 €35,000, and €45,000 was 0.980, 0.992, 0.994, 0.994, and

0.994 in the CRQ Total score analysis compared to 0.000, 0.001, 0.001, 0.003, and 0.007 in the QALYs gained analysis.

**Conclusions:**

While analysis suggests that SEPRP was cost effective if society is willing to pay at least €850 per one-point increase in disease-specific CRQ, no evidence exists when effectiveness was measured in QALYS gained.

Comment [i2]: The findings from the study have now been significantly toned down to reflect the comments by the reviewer.

Abstract altered to meet word count.

**KEY WORDS**:

COPD; Pulmonary Rehabilitation; Structured Education; Cost Effectiveness

**TRIAL REGISTRATION:**

Current Controlled Trials ISRCTN52403063

## INTRODUCTION

Pulmonary rehabilitation is key strategy in the clinical management of chronic obstructive pulmonary disease (COPD) and has been shown to be effective in improving patients' health related quality of life.[1, 2, 3] While much of the established evidence relates to programmes delivered in hospital, outpatient, or home settings,[4,5] there are growing calls for the provision of such services in the primary care setting.[6,7] Nonetheless, further evidence on clinical and cost effectiveness is required before primary care provision can be recommended. The PRINCE study sought to examine the clinical and cost effectiveness of pulmonary rehabilitation for COPD delivered at the level of general practice in Ireland.[8] To this end, the study evaluated a structured education pulmonary rehabilitation programme (SEPRP) intervention based on evidence collected alongside the cluster randomized controlled trial (RCT).[8]. The SEPRP consisted of a two-hour group-based session each week for eight weeks delivered jointly by practice nurses and physiotherapists and was compared in the trial to usual practice in primary care. The primary outcome in the clinical analysis was change in disease-specific health status from baseline to follow up, as measured using the Chronic Respiratory Questionnaire (CRQ) instrument,[9] with results indicating a significant improvement in health status for patients who received the intervention relative to the control of usual care.[10]

In addition to clinical effectiveness, any decision regarding the adoption of a healthcare intervention in clinical practice will depend upon its expected cost effectiveness.[11]The technique of economic evaluation compares the relative cost effectiveness of alternative treatment strategies by relating their mean differences in cost to their mean differences in effectiveness, and by quantifying the uncertainty surrounding these incremental point estimates. Central to this process is the selection of suitable outcome measures which enable the detection of clinically important treatment effects. In addition, and in order to more fully inform priority setting, generic outcome measures are preferable as they enable the comparison of a wide range of programmes across multiple patient populations, all of which may be competing for limited healthcare resources. Notably however, recent evidence has cast doubt on the ability of generic outcome measures to adequately capture meaningful differences in clinical severity for COPD patient populations.[12] Indeed, the adoption of generic rather than disease-specific measures in this context may lead to the underestimation of treatment benefits, biased cost effectiveness results, and ill-informed policy decisions.[13]

With this in mind, we present and compare cost effectiveness and cost utility results for disease-specific health status, as measured by the CRQ, and generic health status, as measured by quality adjusted life years (QALYs) gained.

## METHODS

### The PRINCE Cluster RCT

Full details of the study methods are published elsewhere.[8] In brief, a cluster randomized controlled trial (RCT) recruited 32 general practices and 350 patients with a diagnosis of COPD as defined by the GOLD guidelines.[14] Ethical approval was provided by the local ethics committees at the participating study centres. Practices were randomised to the control group, where patients (n=172) received usual care in general practice, or the intervention group, in which patients (n=178) received a structured education pulmonary rehabilitation programme (SEPRP). The SEPRP consisted of an eight-week programme with a group two-hour session each week delivered jointly by a practice nurse and physiotherapist at the practice surgery or nearby venue. The practice nurse facilitated the educational content of the programme and the physiotherapist focused on delivering the exercise component. The practice nurse also provided on-going advice and support to participants as required throughout the intervention period. In addition, participants were followed-up formally via telephone call at 4 weeks after completion of the SEPRP and via a 1-hour group session at 10 weeks. To facilitate the delivery of the intervention, educators received training via specialised preparation programmes and on-going support from the research team. To ensure standardisation of programme content and delivery, all training was provided by research staff, and educators were audited to ensure adherence to programme principles and content. The control arm in this study was usual care in Irish general practice. However, pulmonary rehabilitation is not currently offered in a systematic manner in primary care in Ireland. A descriptive qualitative analysis revealed that usual care involves patients with COPD attending their GP if they feel unwell and taking their prescribed medications.[10] Indeed, the data we present for the control arm in relation to their healthcare services and medications usage goes to highlight the nature of usual practice in the primary care setting.

Comment [i3]: Usual care is now described in greater detail.

Details on the characteristics of the study participants are presented in Appendix Table 1 and were broadly similar across treatment arms.[10] Two patients in the intervention group and 6 patients in the control group died over the course of the trial and are excluded from the

analysis, leaving 342 (98%) for the statistical analysis.[10] The primary outcome in the clinical analysis was change in disease-specific health status from baseline to follow up, as measured using the CRQ.[9] At trial follow up, the intervention was associated with statistically significant improvements in CRQ Dyspnoea scores (0.49; 95% CIs: 0.20, 0.78), CRQ Physical scores (0.37; 95% CIs: 0.14, 0.60), and CRQ Total score (1.11; 95% CIs: 0.35, 1.87) relative to the control.[10] There were concerns, however, that the confidence intervals did not exclude differences in effect that were pre-specified as clinically insignificant.[10]

**Economic Evaluation**

The economic evaluation consisted of a trial-based analysis with a time horizon of 22 weeks, the trial follow up period. The perspective of the healthcare provider was adopted with respect to costing and health outcomes were expressed in terms of disease-specific and generic health status. Data are also presented for private patient expenses. Evidence on resource use and health status, specifically CRQ and EQ5D, was collected via structured questionnaires and practice note searches at baseline (for the 26 weeks pre-randomisation) and follow up (at 22 weeks post randomisation). Given the length of follow up, neither nether costs nor outcomes were discounted. The statistical analysis was conducted on an intention to treat basis, and in accordance with current guidelines for clinical and cost effectiveness analysis alongside cluster RCTs.[15,16] That is, we adopt statistical techniques which recognise both the clustering and correlation of cost and effect data. The incremental analyses were undertaken using generalised estimating equations (GEE), a flexible multivariate regression framework that explicitly allows for the modelling of normal and non-normal distributional forms of clustered data.[17] Uncertainty in the analysis was addressed by estimating 95% confidence intervals and cost effectiveness acceptability curves, which link the probability of a treatment being cost effective to a range of potential threshold values ($\lambda$) that the health system may be willing to pay for an additional unit of effect.[11] In addition, sensitivity analysis was undertaken to examine the effect of conducting a complete case only analysis and of varying the cost of delivering the intervention in practice. All analysis was undertaken using STATA and EXCEL statistical packages.

**Cost Analysis**

Three cost components were included in the analysis, all of which were expressed in Euros (€) in 2009 prices. The first was the cost of implementing the intervention in clinical practice and included resources relating to: educator and patient recruitment; educator, administrator

and patient time input; venue and equipment rental; educational materials and consumables; and post, packaging, telephone and travel expenses (see Appendix Table 2).These costs were allocated to all 178 patients who participated in the SEPRP intervention. In sensitivity analysis, we explore the effect to expanding the number of patients per SEPRP session from an average of 11 to 15, or 240 in total, and 20, or 320 in total, respectively; thereby reducing the intervention cost per patient.

Second, costs relating to the use of primary and secondary healthcare services over the course of the trial were estimated. This included the costs of general practitioner (GP), practice nurse, physiotherapist, dietician, public health nurse, home help, and social worker consultations, outpatient services, accident and emergency (A&E) visits, hospital admissions, COPD medications and oxygen therapy. Third, private costs to patients, in terms of time input and travel expenses over the course of the trial, were included.

Resource use was captured via a combination of electronic chart searches and patient questionnaires conducted by research staff at baseline and follow up. A vector of unit costs was applied to calculate the cost associated with each resource activity at baseline and follow up (see Table 1). Unit cost estimates for each activity were based on national data sources and, where necessary, were transformed to Euros (€) in 2009 prices using appropriate indices.[18,19] In particular, unit costs per consultation were obtained from published health service documents while drugs were costed using the monthly index of medical specialties for Ireland. Two total cost variables were constructed for the incremental analysis: (i) total healthcare cost and (ii) total patient cost. To facilitate this process, imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing values for individual resource use at follow up. Imputation for resource use was undertaken using the *uvis* command in STATA 11, based on a single imputed dataset, and assuming a non-normal distribution for each dependent variable. While the amount of missing data was very low, we adopted this approach to ensure a more complete analysis. Estimation of incremental costs at follow up was undertaken using GEE regression models controlling for treatment arm, baseline cost, and clustering. To account for the non-normal nature of the cost data, multilevel regression models assuming a gamma variance function were estimated.[20]

**Comment [i4]:** Charts are now identified as electronic.

**Comment [i5]:** The imputation process is now described in more detail.

**Effectiveness Analysis**

Health outcomes in the analysis were expressed in terms of disease-specific and generic measures of health status. COPD-specific health status was measured using the CRQ instrument,[9] which consists of 20 items which are subdivided into four domains: dyspnoea, fatigue, emotional function and mastery. The self-administered version of the CRQ with individualized dyspnea domain was used. Individuals were asked to rate each item on a 7-point scale from 1 (maximum impairment) to 7 (no impairment). Each domain is scored as the sum of the individual items.[9] Based on patient responses, three CRQ aggregate scores can be calculated: (i) CRQ Physical, which is an aggregate of the dyspnoea and fatigue domains; (ii) CRQ Psychological, which is an aggregate of the emotional function and mastery domains; and (iii) CRQ Total, which is an aggregate of all four domains.[9] For the purposes of the economic evaluation, only the CRQ Total score variable was included in the incremental cost effectiveness analysis.

Generic health status was expressed in terms of QALYs gained calculated based on patient responses to the EuroQol EQ5D 3L instrument.[21,22] The EQ5D consists of five dimensions: mobility, self-care, usual activities, pain or discomfort and anxiety or depression; and each dimension has three levels of severity: no problems, moderate problems or extreme problems. EQ5D responses are transformed using an algorithm into a single health state index score, based on values elicited via the time trade-off approach for the UK population,[23,24] which typically range from 0 (equivalent to death) to 1 (equivalent to good health), although a small number of health states are valued as worse than death. EQ5D scores at baseline and follow up were used to calculate patient-specific QALYs gained over 22 weeks using the area under the curve method.[25] Once again, to facilitate this process, imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing values at follow up. Imputation was undertaken using the *uvis* command in STATA 11 and based on a single imputed dataset. Estimation of incremental effectiveness at follow up was undertaken using GEE regression models, assuming a Gaussian variance function, and controlling for treatment arm, baseline EQ5D score, and clustering.

**Comment [i6]:** The imputation process is now described in more detail.

**Cost Effectiveness Analysis**

To undertake the cost effectiveness analysis, we adopt techniques which recognise both the clustering and correlation of cost and effect data collected alongside cluster RCTs. In economic evaluation, one treatment is defined as more cost effective than its comparator if

one of the following conditions apply: (a) it is less costly and more effective; (b) it is more costly and more effective, but its additional cost per additional unit of effect, known as the incremental cost effectiveness ratio (ICER), is considered worth paying by decision makers; or (c) it is less costly and less effective, but the additional cost per additional unit of effect of its comparator is not considered worth paying by decision makers.[11] We employ the net benefit framework,[26] which allows for costs and effectiveness, and their correlation, to be combined into a single variable for each individual, to identify which of these three conditions applies in this case.

We define net benefit (*nb*) as,

$nb_{ijk} = e_{ijk}\lambda - c_{ijk}$,

where $e_{ijk}$ is the health outcome for the $_i$th person in the $_j$th cluster in treatment arm $_k$, $\lambda$ is the cost effectiveness threshold value, and $c_{ijk}$ is their cost. Using this framework, the intervention is defined to be cost effective, at a given threshold value, $\lambda$, if its corresponding net benefit is greater than that of the control: that is, if the incremental net benefit for the intervention minus control is greater than zero.

Net benefit statistics for CRQ Total score and QALYs gained were calculated by relating total healthcare costs to the outcome measures of interest for a series of threshold values (ranging from $\lambda$ = €0 to €70,000). Imputation, conditional on age, gender, and treatment arm, was undertaken to estimate missing CRQ values at follow up. Estimation of incremental net benefit was undertaken using GEE regression models, assuming a Gaussian variance function, and controlling for treatment arm, baseline CRQ or EQ5D score, baseline healthcare cost and clustering. The incremental cost effectiveness results are presented using ICERs and cost effectiveness acceptability curves, which were estimated parametrically,[26] and report the probability that the intervention is more cost effective than the control. The curves incorporate the sampling uncertainty around the ICER estimates as well as the uncertainty around the true threshold value, $\lambda$,[27] which is not explicitly known for Ireland.[28]

**RESULTS**

Raw data estimates for resource use, costs and health outcomes at follow up are summarised in Table 2 (for the equivalent baseline results see Appendix Table 3). Information on missing data is presented in the table footnotes. The cost of the intervention was estimated at €822 per participant, which consisted of €564 in healthcare costs and €258 in patient costs (see Appendix Table 2). Individual resource costs were combined to calculate total costs of care and are presented in Table 3. In terms of total costs over 22 weeks follow up, the mean unadjusted healthcare cost per patient in the control arm was €1505 (SD: 1872) and €2357 (SD: 3532) in the intervention arm. The equivalent results for unadjusted total patient cost over 22 weeks follow up were €129 (SD: 113) and €380 (SD: 111) respectively.

In terms of disease-specific health status, mean unadjusted CRQ Total score per patient at 22 weeks follow up was 19.10 (SD: 4.83) in the control arm and 20.82 (SD: 3.88) in the intervention arm (see Table 3). Further results for CRQ domain scores are presented in Table 2 and in Casey et al.[10] In terms of generic health status, mean unadjusted QALYs gained per patient at 22 weeks was 0.305 (SD: 0.106) in the control arm and 0.337 (SD: 0.081) in the intervention arm (see Table 3).

The results from the incremental analyses are also presented in Table 3. These indicate that the intervention was, on average, associated with higher costs and improved health outcomes, as measured using the CRQ and QALYs, when compared to the control. The intervention was estimated to result in a statistically significant increase in mean cost per patient of €944 (95% CIs: 489, 1400) in total healthcare costs and €261 (95% CIs: 226, 296) in total patient costs. Both estimates were adjusted to account for differences in baseline costs across groups. In respect of effectiveness, the intervention was associated with a statistically significant increase in mean CRQ Total score of 1.11 (95% CIs: 0.35, 1.87) per patient and a non-significant increase in mean QALYs gained of 0.002 (95% CIs: -0.006, 0.011) per patient. Similarly, both estimates were adjusted to account for baseline differences across groups

These results translated into incremental cost effectiveness ratios of €850 per unit increase in CRQ Total score and €472,000 per additional QALY gained. In terms of expected cost effectiveness, the probabilistic results are summarised in Table 3 and presented graphically in Figure 1. These indicate that for the CRQ Total score analysis, the probability of the intervention being more cost effective than the control was 0.980, 0.992, 0.994, 0.994, and 0.994 at threshold values of €5,000, €15,000, €25,000 €35,000, and €45,000 respectively. For

the QALYs gained analysis, the equivalent probability estimates were 0.000, 0.001, 0.001, 0.003, and 0.007 respectively. The results from the sensitivity analysis are presented in the appendix and generally conform to the expected cost effectiveness results reported for the primary analysis.

## DISCUSSION

On the basis of evidence collected alongside a cluster RCT, a structured education pulmonary rehabilitation programme for COPD delivered in primary care was, on average, more costly and more effective than usual general practice care. Notably however, while the intervention was associated with statistically significant improvements in disease-specific health status, this was not reflected in generic health status. Moreover, the confidence intervals for the disease-specific analysis included differences in effect that were deemed clinically insignificant.[10] Given the uncertainty relating to the effectiveness data, there is unsurprisingly conflicting evidence regarding the value for money of the programme. While the cost effectiveness evidence suggests that the programme may be cost effective when outcomes are measured in terms of disease-specific health status and if society is willing to pay at least €850 per one-point increase in CRQ, no such evidence exists in relation to generic health status. More specifically, in the cost per CRQ Total score analysis, the probability that the intervention was more cost effective than usual care was 0.980 or greater for a range of potential threshold values, notwithstanding concerns relating to clinical insignificance. In stark contrast, the cost per QALY gained analysis indicates that the intervention is highly unlikely to be deemed cost effective relative to usual care or indeed other programmes inside and outside of COPD medicine.

The ceiling ratios per QALY gained presented provide a useful range for comparison, given the lack of an implicit or explicit values for Ireland, and the current weak evidence base with respect to this type of health economic analysis for Ireland. However, the approach we used in applying the same ceiling rates per unit increase in CRQ gained is problematic as these values may, or may not, be much lower than those presented. In comparison to countries such as the UK, the range of ceiling ratios presented may be too high for CRQ in particular, and it might have been more useful, if somewhat more cumbersome, to present a different range of ceiling ratios for each of the two outcomes. For example, the shape of the CEAC for CRQ is likely to be different if additional points between €0 and €5,000 were evaluated.

**Comment [i7]:** The findings from the study have now been significantly toned down to reflect the comments by the reviewer.

Indeed the probability of the intervention being more cost effective than the control was 0.087, 0.571, 0.900, and 0.995 at threshold values of €500, €1,000, €2,000 and €4,000 respectively. The difficulty is that in the absence of evidence in regard to an appropriate range of ceiling ratios any decision will appear arbitrary and be open to criticism. As usual, it will ultimately be the responsibility of the relevant policy decision maker to determine whether the evidence presented is sufficient to justify the adoption of the SEPRP intervention in clinical practice. What is clear is that there were significant improvements in CRQ after adjusting for differences in baseline values between intervention and control groups.

**Comment [i8]:** We now include probability estimates for threshold values between 0 and 5000.

This study highlights the complexity of resource allocation decision making in this context as variations in estimated incremental effectiveness have markedly different implications for policy depending on the specificity of the outcome. Indeed, the central question is whether our findings reflect an absence of a clinically significant treatment effect or alternatively a lack of sensitivity in the ability of the generic EQ5D instrument to detect a clinically meaningful improvement in COPD health status. In the case of the former, it is worth noting that in contrast to the majority of trials included in a Cochrane systematic review,[4] most of the participants in our study had moderate COPD (FEV1 around 55-60% predicted).[10] This is not surprising given that the target COPD population in a primary care setting is, by definition, likely to be less severely affected than hospital-based populations. Overall, our results highlight the need for a better understanding of the relationship between COPD disease-specific and generic outcome measures, the importance of exploring cost effectiveness in terms of both disease-specific and generic health status for this patient population, and the need to consider both measures in the resource allocation decision making process. Indeed, our findings can be added to those of existing studies which explore how the adoption of generic rather than disease-specific measures in this context may lead to the underestimation of treatment benefits, biased cost effectiveness results, and ill-informed policy decisions.[12,13] Moreover, this study highlights the difficulty of identifying an appropriate ceiling ratio and drawing conclusions based on ICERs using non-preference-based measures.

That said, our study adds to the existing literature on the cost effectiveness of pulmonary rehabilitation for COPD by evaluating a programme delivered in primary care. There is a broad literature showing that such programmes are cost effective in various hospital, outpatient and home settings [29-37]. Moreover, it also adds to the growing evidence of cost-

effectiveness gains from rehabilitation and self-management programmes delivered in primary care settings for other diseases such as diabetes [38,39] and heart disease.[40] Keeping people out of hospital has been shown to be the key driver in lowering costs in the majority of these studies. Moreover, those studies which have reported cost savings generally adopted time horizons for analysis of one year or more, while we were restricted to a follow up of only 22 weeks. The short-time horizon for our study is, therefore, a significant weakness to exploring the sustainability of the intervention. Extending the time horizon would likely improve the cost-effectiveness of the intervention, linked to lower hospital admissions, if the evidence of other studies can be used as a guide to future resource use in Ireland. It should also be noted that the use of 2009 prices in the analysis may have inflated costs. Medical inflation has fallen in the period since then, which would also likely contribute to an improvement in the cost effectiveness results into the future.

A few other points should be noted as having potential effects on the results of this study. Participants were randomised to control and intervention following the collection of baseline data and the demographic data indicated that both groups were well matched.[10] However, there was no feasible way to blind the intervention group to participants or to those facilitating the programme and the study is open to a risk of performance bias. Nevertheless, outcome assessment was blinded thus minimising risks to detection bias. In addition, patients with very severe COPD were excluded due to concerns for their safety and health risks.[8] This is not unusual for trials, in which obtaining a homogenous sample is prioritised, although it does raise concerns as to the generalizability of the findings presented. From an equity perspective, the programme was delivered free at the point of use to all participants ensuring that no one was excluded on the basis of inability to pay. Importantly, patients who died over the course of the trial were excluded from the statistical analysis. This was a pragmatic decision by study researchers on the basis of the trial follow up being limited to 22 weeks and the need to explicitly avoid ascribing differences across groups to the alternative treatments. While this may introduce bias, we do not believe that it would fundamentally alter the results as presented.

The conduct of economic evaluation in Ireland is complicated by a paucity of relevant data. In particular, given the lack of utility data the EQ5D instrument was adopted and assumed to be relevant for an Irish population. This may not be the case. The process of conducting cost analysis in Ireland is also compromised by the lack of nationally available unit cost data. In

**Comment [i9]:** The discussion section has been altered significantly.

The limitations now include issues raised by the reviewers: generalizability, equity, single trial, imputation, exclusion of dead patients.

estimating unit costs for individual resource activities, we endeavoured at all times to be conservative in any assumptions adopted. Furthermore, while we employ an appropriate multilevel net benefit regression approach to account for the correlation and clustering in the cost and effect data, arguments could be made for alternative bivariate or non-parametric approaches.[16] Moreover, while imputation was deemed necessary for the analysis the approach adopted may be criticised as we imputed values for costs and effects independently. Finally, our analysis is limited by the fact that it is based mainly on data collected using a single trial. While this was deemed sufficient to consider the research question from an Irish perspective, our results would need to be analysed in combination with other international studies to explore the cost effectiveness of pulmonary rehabilitation for COPD in primary care.

In conclusion, the evidence is contradictory in regard to the cost effectiveness of a structured education programme for COPD delivered in primary care in Ireland. While there appears to be evidence in support of the programme if society is willing to pay at least €850 per one-point increase in disease-specific COPD health status, there is no such evidence in relation to generic health status as measured by QALYs. As a result, uncertainty surrounds the policy implications of this analysis. Nonetheless, the study confirms the importance of calculating incremental cost effectiveness results for both disease-specific and generic outcome measures for COPD patient populations.

**Comment [i10]:** The findings from the study have now been significantly toned down to reflect the comments by the reviewer.

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**Table 1 – Categories of Resource Use and Unit Cost Estimates in 2009 (€) Prices**

| RESOURCE ITEM | ACTIVITY | UNIT COST €'s | SOURCE |
|---|---|---|---|
| **Healthcare Resources** | | | |
| General Practitioner Visit | Per Consultation | 50 | ORC |
| Practice Nurse Visit | Per Consultation | 12 | DOHC |
| Hospital Admission Visit | Per Inpatient Day | 832 | DOHC |
| Outpatient Clinic Visit | Per Visit | 169 | DOHC |
| Accident and Emergency Clinic Visit | Per Visit | 289 | DOHC |
| Physiotherapist Visit | Per Consultation | 24 | HSE |
| Dietician Visit | Per Consultation | 24 | HSE |
| Public Health Nurse Visit | Per Consultation | 27 | HSE |
| Home Help Visit | Per Consultation | 16 | HSE |
| Social Worker Visit | Per Consultation | 24 | HSE |
| Spiriva (Tiotropium Bromide) | Per Day | 1.42 | MIMS |
| Seretide (Salmeterol, Fluticasone propionate) | Per Day | 2.22 | MIMS |
| Serevent (Salmeterol xinafoate) | Per Day | 0.94 | MIMS |
| Ventolin (Salbutamol Sulfate, Salamol) | Per Day | 0.24 | MIMS |
| Combivent (Ipratropium Bromide-Salbutamol Sulfate) | Per Day | 0.83 | MIMS |
| Singulair (Montelukast) | Per Day | 1.18 | MIMS |
| Becotide (Beclometasone, Beclazone) | Per Day | 0.27 | MIMS |
| Symbicort (Cortisone Inhalers) | Per Day | 1.55 | MIMS |
| Pulmicort (Budesonide) | Per Day | 0.82 | MIMS |
| Bricanyl (Terbutaline Sulfate) | Per Day | 0.21 | MIMS |
| Oral Prednisone (Prednesol, Deltacortril) | Per Day | 0.47 | MIMS |
| Oral Phyollocntin (Aminophylline) | Per Day | 0.28 | MIMS |
| Uniphyl (Theophylline) | Per Day | 0.19 | MIMS |
| Atrovent (Ipratropium bromide) | Per Day | 0.20 | MIMS |
| Oxygen Cylinder | Per Day | 4.91 | Britton et al, 2003 |
| Oxygen Concentrator | Per Day | 2.19 | Britton et al, 2003 |
| | | | |
| **Patient Resources** | | | |
| *Travel Expenses* | | | |
| Car | Per Mile | 1.06 | DOF |
| Bus | Per Mile | 1.64 | Dublin Bus |
| Taxi | Per Fare/Add. Mile | 3.71/1.56 | www.taxi.ie |
| *Time Input* | | | |
| Economically Active | Per Hour | 19 | CSO |
| Economically Inactive | Per Hour | 9 | CSO |

**Note:**
ORC – Office of the Revenue Commissioner, Dublin, Ireland.
DOHC – Casemix Unit, Department of Health and Children, Dublin, Ireland
HSE – Salary Scales, Health Service Executive, Dublin, Ireland
MIMS - Monthly Index of Medical Specialties Ireland, Dublin, Ireland
DOF – Department of Finance, Dublin, Ireland
CSO – Central Statistics Office, Dublin, Ireland

**Table 2 – Raw Data Estimates at Follow Up for Resource Use and Costs (both estimated for the 22 weeks following randomisation) and Health Outcomes.**

**Comment [i11]:** Table 2 has been altered to meet the suggestions of the reviewers: (healing and footnotes)

| VARIABLE | INTEVENTION (N=178) *Mean (SD) / %* | | CONTROL (N=172) *Mean (SD) / %* | |
|---|---|---|---|---|
| **RESOURCE ITEM** | **Usage** | **Cost (€)** | **Usage** | **Cost(€)** |
| **Healthcare Resources** | | | | |
| GP Visits: Breathing Problems | 1.6 (2.0) | 134 (122) | 1.8 (2.5) | 153 (158) |
| GP Visits: Other | 2.4 (2.5) | 118 (124) | 2.7 (2.7) | 133 (136) |
| Practice Nurse Visits: Breathing Problems | 0.1 (0.3) | 1 (4) | 0.1 (0.5) | 2 (6) |
| Practice Nurse Visits: Other | 1.1 (2.0) | 13 (24) | 1.2 (2.1) | 14 (25) |
| Inpatient Days: Breathing Problems | 0.5 (2.8) | 411 (2300) | 0.1 (0.6) | 80 (504) |
| Inpatient Days: Other | 0.4 (2.5) | 336 (2054) | 0.3 (1.9) | 266 (1552) |
| Outpatient Visits: Breathing Problems | 0.2 (0.5) | 36 (90) | 0.3 (0.7) | 52 (124) |
| Outpatient Visits: Other | 0.8 (1.5) | 134 (253) | 0.7 (1.2) | 118 (208) |
| Accident &Emergency Visits: Breathing Problems | 0.1 (0.2) | 12 (57) | 0.1 (0.3) | 17 (76) |
| Accident &Emergency Visits: Other | 0.1 (0.3) | 23 (78) | 0.1 (0.2) | 16 (66) |
| Physiotherapist Visits: Breathing Problems | 0.3 (1.4) | 6 (33) | 0.2 (1.3) | 5 (30) |
| Physiotherapist Visits: Other | 0.5 (1.9) | 11 (46) | 0.5 (1.9) | 11 (45) |
| Public Health Nurse Visits: Breathing Problems | 0.1 (1.0) | 3 (27) | 0.1 (1.0) | 3 (28) |
| Public Health Nurse Visits: Other | 0.3 (1.6) | 8 (42) | 0.4 (1.9) | 12 (51) |
| Dietician Visits | 0.0 (0.2) | 1(4) | 0.0 (0.3) | 1 (6) |
| Home Help Visits | 3.9 (17.5) | 63(280) | 5.4 (20.3) | 87 (325) |
| Social Worker Visits | 0.0 (0.0) | 0 (0) | 0.0 (0.1) | 1 (2) |
| Spiriva | 59% | 138 (115) | 62% | 144 (113) |
| Seretide | 56% | 203 (182) | 55% | 200 (182) |
| Serevent | 1% | 2 (16) | 1% | 1 (12) |
| Ventolin | 53% | 21 (20) | 52% | 20 (20) |
| Combivent | 13% | 18 (46) | 15% | 21 (49) |
| Singulair | 9% | 16 (53) | 11% | 21 (60) |
| Becotide | 4% | 2 (9) | 7% | 3 (11) |
| Symbicort | 18% | 45 (97) | 20% | 50 (102) |
| Pulmicort | 4% | 5 (26) | 5% | 7 (30) |
| Bricanyl | 2% | 1 (5) | 2% | 1 (5) |
| Oral Prednisone | 4% | 3 (15) | 11% | 8 (24) |
| Oral Phyollocntin | 1% | 1 (4) | 3% | 1 (8) |
| Uniphyl | 8% | 3 (8) | 7% | 2 (8) |
| Atrovent | 7% | 2 (8) | 8% | 3 (9) |
| Oxygen Therapy | 3% | 16 (96) | 5% | 26 (121) |
| Intervention | n/a | 564 (n/a) | n/a | 0 (n/a) |
| | | | | |
| **Patient Resources** | | | | |
| Travel Expenses | n/a | 88 (89) | n/a | 86 (80) |
| Time Input | n/a | 37 (32) | n/a | 39 (32) |
| Intervention | n/a | 258 (n/a) | n/a | 0 (n/a) |
| **HEALTH OUTCOME** | | | | |
| **Disease Specific Measure** | | | | |
| CRQ Dyspnea Score | 4.42 (1.36) | | 3.85 (1.45) | |
| CRQ Fatigue Score | 4.79 (1.31) | | 4.33 (1.47) | |
| CRQ Emotional Score | 5.62 (1.19) | | 5.24 (1.30) | |
| CRQ Mastery Score | 5.94 (1.11) | | 5.59 (1.30) | |
| CRQ Physical Score | 4.62 (1.10) | | 4.12 (1.29) | |
| CRQ Psychological Score | 5.78 (1.06) | | 5.41 (1.22) | |
| | | | | |
| **Generic Measure** | | | | |
| EQ5D Score | 0.801 (0.232) | | 0.762 (0.252) | |

**Note 1:** Raw data have not been adjusted for baseline values and do not include imputations for missing values.
**Note 2:** Eight patients (6 intervention and 2 control) who died over the course of the study were excluded from the analysis. Completeness of cost data: ***Intervention*** - 99% for on primary care utilisation, 99% for secondary care utilisation, 80% for community care utilisation, 99% for medication utilisation, 80% for oxygen therapy utilisation, and 78% for Total Healthcare Cost. ***Control***: 97% 97%, 78%, 97%, 78% and 78% respectively. Completeness of effect data: ***Intervention*** - 80% for CRQ, 80% for EQ5D and 80% for QALY scores. ***Control*** - 78%, 78% and 78% (N=134) respectively.

**Table 3 – Incremental Cost Effectiveness Results**

| **COST ANALYSIS** | **INTEVENTION (N=178)** *Mean (SD)* | **CONTROL (N=172)** *Mean (SD)* |
|---|---|---|
| **Healthcare Resources** Total Healthcare Cost per patient (€) | 2357 (3532) | 1505 (1872 |
| **Patient Resources** Total Patient Cost per patient (€) | 380 (111) | 129 (113) |
| | **Incremental Analysis** **Difference in Means (95% CI's) [p-value]** (Intervention versus Control) | |
| **Healthcare Resources** Total Healthcare Cost per patient (€) | 944 (489, 1400) [<0.01] | |
| **Patient Resources** Total Patient Cost per patient (€) | 261 (226, 296) [<0.01] | |
| | | |
| **EFFECTIVENESS ANALYSIS** | **INTEVENTION (N=178)** *Mean (SD)* | **CONTROL (N=172)** *Mean (SD)* |
| **Disease Specific Measures** CRQ Total Score | 20.82 (3.88) | 19.10 (4.83) |
| **Generic Measures** QALYs gained | 0.337 (0.081) | 0.305 (0.106) |
| | **Incremental Analysis** **Difference in Means (95% CI's)[p-value]** (Intervention versus Control) | |
| **Disease Specific Measures** CRQ Total Score | 1.11 (0.35, 1.87) [<0.01] | |
| **Generic Measures** QALYs gained | 0.002 (-0.006, 0.011) [0.63] | |
| | | |
| **COST EFFECTIVENESS ANALYSIS** | **Incremental Cost Effectiveness Ratios** (Difference in Mean Cost / Difference in Mean Effect) | |
| **Disease Specific Measures** Cost per CRQ Total Score (€) | 850 | |
| **Generic Measures** Cost per QALYs gained (€) | 472,000 | |

**Probability that the Intervention is Cost Effective at Threshold Value (λ)**

| **Threshold Value (λ)** | **CRQ Total** | **QALYs gained** |
|---|---|---|
| **λ = €5,000** | 0.980 | 0.000 |
| **λ = €15,000** | 0.992 | 0.001 |
| **λ = €25,000** | 0.994 | 0.001 |
| **λ = €35,000** | 0.994 | 0.003 |
| **λ = €45,000** | 0.994 | 0.007 |

**Note 1**: Reported estimates for total costs, CRQ and QALYs include imputed values for missing data.
**Note 2**: Reported estimates for incremental differences in costs and effects adjusted to account for baseline difference between groups.
**Note 3:** Regression models for total costs analyses estimated using GEE models assuming Gamma variance function, identify link function, exchangeable correlation, and controlling for treatment arm, baseline value, clustering.
**Note 4:** Regression models for CRQ, QALYs and Net Benefit estimated using GEE models assuming Gaussian variance function, identify link function, exchangeable correlation, and controlling for treatment arm, baseline value, and clustering.
**Note 5**: Incremental cost effectiveness analyses adopt healthcare provider perspective and exclude private patient costs.
**Note 6**: Probabilities for cost effectiveness **e**stimated parametrically using net benefit regression models for analysis at each level of **λ.**

**Comment [i12]:** Table 3 has been altered to meet the suggestions of the reviewers: (footnotes)

**Figure 1 - Cost Effectiveness Acceptability Curves**

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**Contributors**

Kathy Murphy, Dympna Casey, Declan Devane, Bernard McCarthy, Adeline Cooney, Lorraine Mee, Collete Kirwan conceived the study and together with John Newell and O'Shea participated in the design of the trial and intervention. Paddy Gillespie and Eamon O'Shea undertook the acquisition, analysis and interpretation of the health economic data and the drafting of the research article. All authors participated in critical revision of the manuscript, and have approved the final version.

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**Ethical approval**

Ethical approval has been granted by the Research Ethics Committee of the National University of Ireland, Galway and the Irish College of General Practitioners (ICGP).

**Competing Interests**

The authors report no competing interests. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: that a research grant from the Health Research Board, Ireland was received to undertake the study, and an unconditional Educational Grant was obtained from Pfizer which provided support services to cover desk-top publication costs for manuals, and support for spirometery. The funders had no part in the design of the study; the collection, analysis, and interpretation of the data; the writing of the report; and the decision to submit the article for publication. All authors declare that no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Data sharing**:

No additional data are available.

**EVEREST Statement**: Checklist for Health Economics Paper:

**Title:** The cost effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial.

| | **Study section** | **Additional remarks** |
|---|---|---|
| **Study design** | | |
| (1) The research question is stated | In Abstract and in the Introduction (pg6) | |
| (2) The economic importance of the research question is stated | In the Introduction (pg 6) | |
| (3) The viewpoint(s) of the analysis are clearly stated and justified | In the Methods: Overview (pg6) | |
| (4) The rationale for choosing the alternative programmes or interventions compared is stated | In the Introduction (pg 5) | As the study is conducted alongside a trial – the alternatives were specified by the trial. |
| (5) The alternatives being compared are clearly described | In the Introduction (pg 5) | |
| (6) The form of economic evaluation used is stated | In the Introduction (pg 5), and in the Methods (pg 7) | We present both CEA and CUA as we use two outcome measures. |
| (7) The choice of form of economic evaluation is justified in relation to the questions addressed | We justify the methods used in the Introduction (pg 6) and the Discussion (10-12) | . |
| | | |
| **Data collection** | | |
| (8) The source(s) of effectiveness estimates used are stated | In the Methods (pg 6-9) | |
| (9) Details of the design and results of effectiveness study are given (if based on single study) | In the Introduction (pg 5-6) and in the Methods (pg 6-9) | |
| (10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies) | N/A | The analysis is based on a single trial |
| (11) The primary outcome measure(s) for the economic evaluation are clearly stated | In the Methods (pg 6-9) | |
| (12) Methods to value health states and other benefits are stated | In the Methods (pg 6-9) | |
| (13) Details of the subjects from whom valuations were obtained are given | In the Methods (pg 6-9) | |

| | | |
|---|---|---|
| (14) Productivity changes (if included) are reported separately | N/A | |
| (15) The relevance of productivity changes to the study question is discussed | N/A | |
| (16) Quantities of resources are reported separately from their unit costs | In Table 2 | |
| (17) Methods for the estimation of quantities and unit costs are described | In the Methods (pg 6-9) and in Table 1 | |
| (18) Currency and price data are recorded | In the Methods (pg6-9) and in Tables 1-3 | |
| (19) Details of currency of price adjustments for inflation or currency conversion are given | In the Methods (pg 6-9) | |
| (20) Details of any model used are given | N/A | |
| (21) The choice of model used and the key parameters on which it is based are justified | N/A | |
| | | |
| **Analysis and interpretation of results** | | |
| **(**22) Time horizon of costs and benefits is stated | In the Methods (pg 6) | Based on the follow up of the trial |
| (23) The discount rate(s) is stated | N/A | Given the length of follow up in the trial |
| (24) The choice of rate(s) is justified | N/A | |
| (25) An explanation is given if costs or benefits are not discounted | N/A | |
| (26) Details of statistical tests and confidence intervals are given for stochastic data | In the Results (pg 9-10) and in Table 3 | |
| (27) The approach to sensitivity analysis is given | In the Methods (pg 8-9) and in Table 3 and Figure 1. | CEACs |
| (28) The choice of variables for sensitivity analysis is justified | N/A | |
| (29) The ranges over which the variables are varied are stated | N/A | |
| (30) Relevant alternatives are compared | In the Results (pg 9-10) and in Table 3 and Figure 1 | |
| (31) Incremental analysis is reported | In the Results (pg 9-10) and in Table 3 and Figure 1 | |
| (32) Major outcomes are presented in a disaggregated as well as aggregated form | In Tables 2 and 3 | |
| (33) The answer to the study question is given | In the Discussion (pg 10-12) | |
| (34) Conclusions follow from the data reported | In the Discussion (pg 10-12) | |

| | | |
|---|---|---|
| (35) Conclusions are accompanied by the appropriate caveats | In the Discussion (pg 10-12) | |

**Appendix Table 1 - Characteristics of clusters (general practices) and baseline demographic and clinical characteristics of COPD patients assigned to intervention (SEPRP) or continued usual care. Values are numbers (percentages) unless stated otherwise (Casey et al, 2013)**

| Characteristics | Intervention (n=178) | Control (n=172) |
|---|---|---|
| No of clusters* | 16 | 16 |
| Median (range) of participants per cluster | 11 (8-14) | 10 (9-14) |
| GP Practice (cluster) | | |
| Urban | 32 (18.0) | 61 (35.5) |
| Rural | 146 (82.0) | 111 (64.5) |
| < 5,000 patients | 88 (49.4) | 64 (37.2) |
| > 5,000 patients | 90 (50.6) | 108 (62.8) |
| Mean (SD) age (years) | 68.8 (10.2) | 68.4 (10.3) |
| Gender | | |
| Male (n, %) | 117 (65.7) | 106 (61.6) |
| Female (n, %) | 61 (34.3) | 66 (38.4) |
| Marital status: | | |
| Married/Living with partner | 111 (62.4) | 115 (66.9) |
| Separated /Divorced | 15 (8.4) | 10 (5.8) |
| Widowed | 26 (14.6) | 21 (12.2) |
| Single / Never married | 26 (14.6) | 26 (15.1) |
| Medical Card Holder | 141 (79.2) | 152 (88.4) |
| Employment status: | | |
| Paid Work: Employee | 17 (9.6) | 12 (7.0) |
| Paid Work: Self employed | 14 (7.9) | 8 (4.7) |
| Homemaker | 26 (14.6) | 19 (11.0) |
| Unemployed looking for work | 8 (4.5) | 8 (4.7) |
| Retired- | 92 (51.7) | 111 (64.5) |
| Unable to work disability | 16 (9.0) | 9 (5.2) |
| Other | 5 (2.8) | 5 (2.9) |
| Spirometry (post-bronchodilator): | | |
| FEV1(% Predicted) [mean (SD)] | 57.6 (14.3) | 59.7 (13.8) |
| FEV1/FVC [mean (SD)] | 52.9 (11.5) | 55.4 (11.9) |
| • GOLD 3 Severe COPD** n=97 (27.7%) | 56 (31.5%) | 41 (23.8%) |
| • GOLD 2 Moderate COPD** n=253 (72.3%) | 122 (68.5%) | 131(76.2%) |
| Patient history (from medical records) | | |
| Hypertension or High Cholesterol | 66 (37.1) | 76 (44.2) |
| Cardiovascular disease | 41 (23.0) | 62 (36.0) |
| Muscoskeletal problems | 66 (37.1) | 73 (42.4) |
| Diabetes | 22 (12.4) | 28 (16.3) |
| Asthma | 38 (22.1) | 41 (23.0) |
| Gastrointestinal disorders | 43 (24.2) | 46 (26.7) |
| CNS Disorders | 18 (10.1) | 21 (12.2) |
| Mental health problems | 28 (15.7) | 27 (15.7) |
| Use of inhalers | 155 (87.1) | 158 (91.9) |
| Home oxygen | 6 (3.4) | 11 (6.4) |
| Never smoked | 16 (9.0) | 27 (15.7) |
| Current smoker (n, %) | 70 (39.3) | 59 (34.3) |
| • Males currently smoking (n, %) | 44 (37.6%) | 33 (31.1%) |
| • Females currently smoking (n, %) | 26 (42.6%) | 26 (39.4%) |

**Note:** * Clusters = GP Practice; ** Classification of COPD based on the GOLD criteria; SD = Standard Deviation

**Appendix Table 2 – Intervention Costs**

| Resource item | | Total Cost |
|---|---|---|
| **Physiotherapist and Practice Recruitment**<br><br>Research Team Time Input; Documentation; Phone Calls, Postage & Packaging | | €688 |
| **Physiotherapist Preparation Programme**<br><br>Research Team Time Input; Participant Time Input; Venue & Equipment Rental; Educational/Training Materials & Consumables; Travel Expenses; Documentation; Phone Calls, Postage & Packaging | | €8,691 |
| **Practice Nurse Preparation Programme**<br><br>Research Team Time Input; Participant Time Input; Venue & Equipment Rental; Educational/Training Materials & Consumables; Travel Expenses; Documentation; Phone Calls, Postage & Packaging | | €24,588 |
| **Patient Recruitment**<br><br>Research Team Time Input; Practice Nurse Time Input; Spirometry Tests, Documentation; Phone Calls, Postage & Packaging | | €11,942 |
| **SEPRP Intervention**<br><br>Physiotherapist and Practice Nurse Time Input; Research Team Time Input; Participant Time Input; Venue & Equipment Rental; Educational/Training Materials & Consumables; Travel Expenses; Documentation; Phone Calls, Postage & Packaging | | €100,483 |
| | | |
| **Total Cost** | | **€146,391** |
| **Total Cost Per Patient (*n=178 patients*)** | | **€822** |
| | **Total Healthcare Cost Per Patient** | **€564** |
| | **Total Private Patient Cost per Patient** | **€258** |

**Note:** Total Healthcare Cost Per Patient used for incremental cost effectiveness analysis

**Appendix Table 3 – Raw Data Estimates at Baseline for Resource Use and Costs (both estimated for the 26 weeks leading up to randomisation) and Health Outcomes.**

**Comment [i1]:** Table 2 has been altered to meet the suggestions of the reviewers: (healing and footnotes)

| VARIABLE | INTEVENTION (N=178) *Mean (SD) / %* | | CONTROL (N=172) *Mean (SD) / %* | |
|---|---|---|---|---|
| **RESOURCE ITEM** | **Usage** | **Cost (€)** | **Usage** | **Cost(€)** |
| **Healthcare Resources** | | | | |
| GP Visits: Breathing Problems | 1.6 (1.7) | 78 (87) | 1.9 (2.8) | 95 (138) |
| GP Visits: Other | 2.7 (2.5) | 135 (123) | 3.2 (3.4) | 159 (171) |
| Practice Nurse Visits: Breathing Problems | 0.3 (0.9) | 3 (11) | 0.2 (0.7) | 2 (8) |
| Practice Nurse Visits: Other | 1.2 (2.2) | 14 (27) | 1.1 (1.8) | 13 (22) |
| Inpatient Days: Breathing Problems | 0.3 (1.2) | 224 (999) | 0.3 (1.5) | 266 (1219) |
| Inpatient Days: Other | 0.7 (4.2) | 538 (3461) | 0.3 (1.3) | 247 (3461) |
| Outpatient Visits: Breathing Problems | 0.3 (0.5) | 44 (90) | 0.5 (1.0) | 90 (167) |
| Outpatient Visits: Other | 0.9 (1.4) | 147 (237) | 1.0 (1.7) | 166 (278) |
| Accident &Emergency Visits: Breathing Problems | 0.1 (0.2) | 13 (60) | 0.1 (0.4) | 29 (116) |
| Accident &Emergency Visits: Other | 0.1 (0.4) | 31 (113) | 0.1 (0.3) | 24 (91) |
| Physiotherapist Visits: Breathing Problems | 0.5 (2.3) | 13 (55) | 0.4 (2.0) | 10 (47) |
| Physiotherapist Visits: Other | 0.7 (2.5) | 16 (60) | 0.6 (2.4) | 15 (58) |
| Public Health Nurse Visits: Breathing Problems | 0.1 (0.4) | 2 (10) | 0.5 (2.1) | 13 (57) |
| Public Health Nurse Visits: Other | 0.4 (1.9) | 11 (52) | 0.7 (2.6) | 19 (69) |
| Dietician Visits | 1.0 (3.2) | 24 (77) | 0.1 (0.4) | 2 (9) |
| Home Help Visits | 5.4 (22.1) | 86 (354) | 7.8 (26.3) | 125 (420) |
| Social Worker Visits | 0.0 (0.1) | 1 (3) | 0.0 (0.1) | 1 (3) |
| Spiriva | 55% | 141 (129) | 62% | 161 (126) |
| Seretide | 49% | 201 (204) | 58% | 234 (201) |
| Serevent | 2% | 3 (22) | 1% | 1 (13) |
| Ventolin | 53% | 23 (22) | 51% | 22 (22) |
| Combivent | 14% | 21 (53) | 15% | 23 (55) |
| Singulair | 7% | 15 (54) | 9% | 19 (61) |
| Becotide | 7% | 3 (12) | 5% | 2 (10) |
| Symbicort | 17% | 49 (107) | 20% | 56 (113) |
| Pulmicort | 3% | 4 (25) | 3% | 4 (25) |
| Bricanyl | 1% | 1 (4) | 2% | 1 (5) |
| Oral Prednisone | 6% | 5 (21) | 9% | 8 (25) |
| Oral Phyollocntin | 1% | 1 (4) | 2% | 1 (7) |
| Uniphyl | 7% | 3 (9) | 7% | 2 (9) |
| Atrovent | 7% | 2 (9) | 6% | 2 (9) |
| Oxygen Therapy | 3% | 22 (118) | 6% | 31 (139) |
| | | | | |
| **Patient Resources** | | | | |
| Travel Expenses | n/a | 109 (93) | n/a | 128 (115) |
| Time Input | n/a | 48 (35) | n/a | 59 (50) |
| | | | | |
| **Total Healthcare Cost** | n/a | 1870 (3855) | n/a | 1850 (2140) |
| **Total Patient Cost** | n/a | 164 (129) | n/a | 181 (159) |
| **HEALTH OUTCOME** | | | | |
| **Disease Specific Measures** | | | | |
| CRQ Dyspnea Score | 3.74 (1.20) | | 3.45 (1.39) | |
| CRQ Fatigue Score | 4.33 (1.31) | | 4.05 (1.48) | |
| CRQ Emotional Score | 5.39 (1.22) | | 5.01 (1.34) | |
| CRQ Mastery Score | 5.42 (1.31) | | 5.25 (1.38) | |
| CRQ Physical Score | 4.09 (1.12) | | 3.77 (1.23) | |
| CRQ Psychological Score | 5.41 (1.16) | | 5.13 (1.26) | |
| **CRQ Total Score** | 19.03 (4.16) | | 17.80 (4.56) | |
| | | | | |
| **Generic Measures** | | | | |
| EQ5D Score | 0.789 (0.209) | | 0.694 (0.296) | |

**Note:** Completeness of cost data: ***Intervention*** - 100% for primary care utilisation, 100% for secondary care utilisation, 100% for community care utilisation, 100% for medication utilisation, and 100% for oxygen therapy utilisation. ***Control***: 100%, 74%, 100%, 100%, 100% and 100% respectively. **Note 1:** Completeness of effect data: ***Intervention*** 100% for CRQ and 100% for EQ5D scores. ***Control***: 100% and 100% respectively.

**Appendix Table 4 Sensitivity Analysis 1 - Complete Case Analysis**

| COST EFFECTIVENESS ANALYSIS | Incremental Cost Effectiveness Ratios (Difference in Mean Cost / Difference in Mean Effect) | |
|---|---|---|
| **Disease Specific Measures** Cost per CRQ Total Score (€) | 660 | |
| **Generic Measures** Cost per QALYs gained (€) | 871,000 | |
| **Probability that the Intervention is Cost Effective at Threshold Value (λ)** | | |
| **Threshold Value (λ)** | **CRQ Total** | **QALYs gained** |
| **λ = €5,000** | 0.981 | 0.000 |
| **λ = €15,000** | 0.992 | 0.000 |
| **λ = €25,000** | 0.994 | 0.000 |
| **λ = €35,000** | 0.994 | 0.000 |
| **λ = €45,000** | 0.995 | 0.001 |

**Appendix Table 5 Sensitivity Analysis 2 - Intervention Cost €418 (15 patients per session)**

| COST EFFECTIVENESS ANALYSIS | Incremental Cost Effectiveness Ratios (Difference in Mean Cost / Difference in Mean Effect) | |
|---|---|---|
| **Disease Specific Measures** Cost per CRQ Total Score (€) | 725 | |
| **Generic Measures** Cost per QALYs gained (€) | 402,500 | |
| **Probability that the Intervention is Cost Effective at Threshold Value (λ)** | | |
| **Threshold Value (λ)** | **CRQ Total** | **QALYs gained** |
| **λ = €5,000** | 0.983 | 0.001 |
| **λ = €15,000** | 0.993 | 0.001 |
| **λ = €25,000** | 0.994 | 0.003 |
| **λ = €35,000** | 0.994 | 0.006 |
| **λ = €45,000** | 0.995 | 0.012 |

**Appendix Table 6 Sensitivity Analysis 3 - Intervention Cost €313 (20 patients per session)**

| COST EFFECTIVENESS ANALYSIS | Incremental Cost Effectiveness Ratios (Difference in Mean Cost / Difference in Mean Effect) | |
|---|---|---|
| **Disease Specific Measures** Cost per CRQ Total Score (€) | 636 | |
| **Generic Measures** Cost per QALYs gained (€) | 353,000 | |
| **Probability that the Intervention is Cost Effective at Threshold Value (λ)** | | |
| **Threshold Value (λ)** | **CRQ Total** | **QALYs gained** |
| **λ = €5,000** | 0.985 | 0.002 |
| **λ = €15,000** | 0.993 | 0.004 |
| **λ = €25,000** | 0.994 | 0.007 |
| **λ = €35,000** | 0.994 | 0.013 |
| **λ = €45,000** | 0.995 | 0.024 |

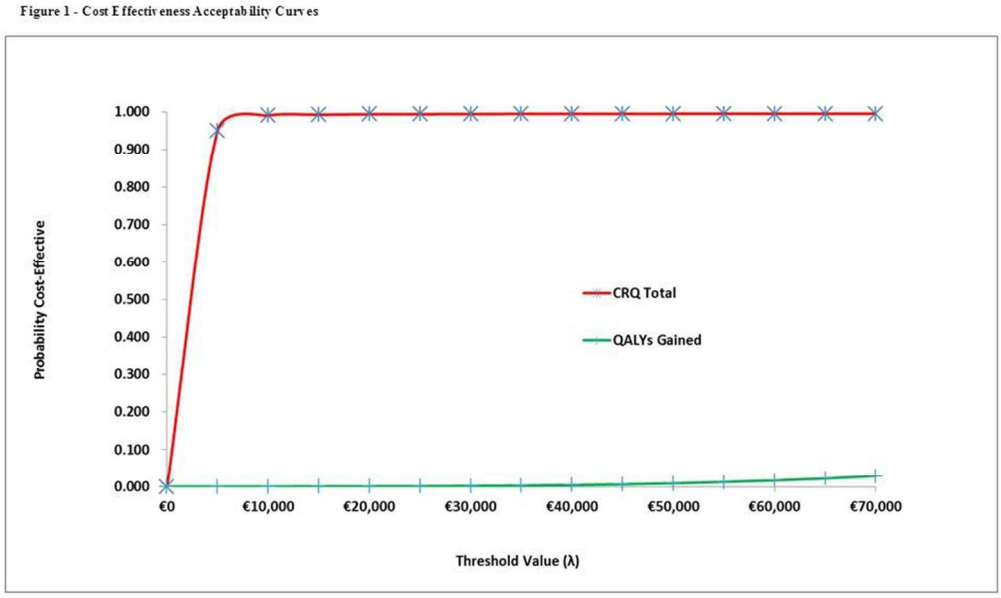


Figure 1: Cost Effectiveness Acceptability Curves
254x190mm (96 x 96 DPI)